08758579 96098219 PMID: 8555367
Fusion of negatively-charged **liposomes** under the effect of peptides from the N-terminal fragment of the HIV-1 transmembrane protein]
Sliianie otritsatel'no zariazhennykh liposom pod deistviem peptidov iz N-kontsevogo fragmenta transmembrannogo belka VICh-1.
Terletskaia Ia T; Trikash I O; Serdiuk E S; Andreev S M
Biokhimii a (Moscow, Russia) (RUSSIA) Oct **1995**, 60 (10) p1711-9, ISSN 0320-9725 Journal Code: 0372667
Document type: Journal Article ; English Abstract
Languages: RUSSIAN
Main Citation Owner: NLM
Record type: Completed
The effect of a series of synthetic peptides mimicking the N-terminus of HIV transmembrane glycoprotein (gp41) on fusion of negatively charged **liposomes** consisting of phosphatidylcholine, phosphatidylethanolamine and cardiolipin at a 2:3:5 molar ratio, respectively, has been studied. Peptides P514 and P385 (residue 517-538), lysine and arginine at the C-terminus, respectively, with the amino acid sequence completely corresponding to the N-terminus of gp41 displayed the highest fusogenic activity. The extent of fusion was significantly increased at mild acidic pH (6.0). Acidification particularly influenced the fusogenic activity of P514. **Modification** of the N- and C-termini of fusion-active peptides by proteins and synthetic **polymers** blocked the fusion activity. The fusogenic properties of peptides depended on the chain length: P411 consisting of nine hydrophobic amino acid residues had no fusogenic activity, while P415, an 11-member peptide, effectively fused **liposomes** . The fluorescent probe ANS was used to monitor the hydrophobicity of these peptides. The hydrophobicity of P514 increased appreciably with a change in pH from 6.0 to 7.5. Peptides P514 and P385 induced the leakage of the aqueous contents from **liposomes** at neutral pH and caused a small, but detectable leakage at acidic pH. Structural and molecular factors influencing the peptide-induced **liposome** fusion are discussed.

3/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08736376 96079213 PMID: 8537880
New synthetic amphiphilic **polymers** for steric protection of **liposomes** in vivo.
Torchilin V P; Trubetskoy V S; Whiteman K R; Caliceti P; Ferruti P; Veronese F M
Department of Radiology, Massachusetts General Hospital, Charlestown, USA.
Journal of pharmaceutical sciences (UNITED STATES) Sep **1995**, 84 (9) p1049-53, ISSN 0022-3549 Journal Code: 2985195R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Carboxy group-terminated synthetic **polymers**--branched poly(ethylene glycol), poly(acryloylmorpholine), and poly(vinylpyrrolidone)--were made amphiphilic by derivatization with phosphatidyl ethanolamine via the terminal carboxy group and then incorporated into lecithin-cholesterol **liposomes** prepared by the detergent dialysis method. Following the biodistribution of **liposomes** in mice, all three **polymers** were shown to be effective steric protectors for **liposomes** and were able to sharply increase **liposome** circulation times in a concentration-dependent manner. The accumulation of **liposomes** in the liver decreases. The effects observed are similar to those found for **liposomes modified** with linear poly(ethylene glycol). At low **polymer** concentration, amphiphilic branched poly(ethylene glycol) seems to be the most effective **liposome** protector, most probably,

```
ILIGHT set on as ' '
? b 155, 5
       25jul02 11:15:25 User242957 Session D456.2
            $0.00    0.072 DialUnits File410
     $0.00  Estimated cost File410
     $0.01  TELNET
     $0.01  Estimated cost this search
     $0.01  Estimated total session cost   0.228 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R)  1966-2002/Jul W3
  File   5:Biosis Previews(R)  1969-2002/Jul W3
         (c) 2002 BIOSIS

      Set  Items  Description
      ---  -----  -----------
? s liposome? and polymer? and modif?
          48168  LIPOSOME?
         488485  POLYMER?
         614444  MODIF?
      S1    239  LIPOSOME? AND POLYMER? AND MODIF?
? s s1 and py<1997
Processing
            239  S1
       19954024  PY<1997
      S2     91  S1 AND PY<1997
? rd
...examined 50 records  (50)
...completed examining records
      S3     68  RD (unique items)
? t s3/3,ab/all

 3/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09492111   97421296   PMID: 9275724
    Effect of membrane modification by PEG on prolongation of
circulation time of liposomes in blood in vivo]
  Hou X P; Zhang J M; Lu X D
  Department of Physical Chemistry, Beijing Medical University.
  Yao xue xue bao = Acta pharmaceutica Sinica (CHINA)   1996,  31
 (6)  p451-4,  ISSN 0513-4870   Journal Code: 21710340R
  Document type: Journal Article ; English Abstract
  Languages: CHINESE
  Main Citation Owner: NLM
  Record type: Completed
  PEG-PE  (polyethylene glycol-phosphatidyl ethanolamine) of different
molecular weight (2000 and 5000) were used to modify the membrane of
liposomes. Large unilamellar liposomes containing PEG-PE were
prepared by reversed phase evaporation. Fluorescent label-calcein was
encapsulated at the internal water phase. To compare the differance between
the modified and unmodified membrane, the stability in vitro and
distribution in vivo were investigated. The results indicated that the
circulation half-life for liposomes unmodified, modified by PEG
(2000)-PE and modified by PEG (5000)-PE were 13, 21 and 75 (min)
respectively. At 6 h after injection, the ratio b/R (b: distribution in
blood, R: distribution in liver and spleen) were 0, 0.8 and 1.4,
respectively. The results mean that the stability increased and circulation
time was prolonged by the PEG-PE modified membrane. The effect of
PEG-PE on membrane was found to be directly proportional to the chain
length of the polymer.


 3/3,AB/2     (Item 2 from file: 155)
```

DIALOG(R)File 155:MEDLINE(R)

09203906 97096895 PMID: 8941716
Lipobeads: a hydrogel anchored lipid vesicle system.
Jin T; Pennefather P; Lee P I
Faculty of Pharmacy, University of Toronto, Ont., Canada.
FEBS letters (NETHERLANDS) Nov 11 **1996**, 397 (1) p70-4, ISSN 0014-5793 Journal Code: 0155157
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A new vesicle system is described that combines complementary properties of **liposomes** and **polymeric** beads. 'Lipobeads' consist of a lipid bilayer shell anchored on the surface of a hydrogel **polymer** cores which acts like a cytoskeleton. Anchoring is provided by fatty acids covalently attached to the surface of the hydrogel. These hydrophobic chains drive spontaneous assembly of a lipid bilayer shell around the **modified** hydrogel bead when exposed to a suspension of **liposomes** . The bilayer is stable and acts as a permeability barrier to compound loaded by prior absorption into the **polymer** core. Lipid mobility in the shell is similar to that found in other unanchored lipid bilayers. The system has potential application in drug delivery and for functional reconstitution of membrane proteins.

3/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09201852 97111888 PMID: 8984475
[Problems in creating insulin preparations with increased stability against proteolysis]
Problemy sozdaniia preparatov insulina s povyshennoi ustoichivost'iu k proteolizu.
Valuev L I; Valuev I L; Sytov G A
Prikladnaia biokhimiia i mikrobiologiia (RUSSIA) Jul-Aug **1996**, 32 (4) p371-81, ISSN 0555-1099 Journal Code: 0023416
Document type: Journal Article; Review; Review, Tutorial ; English Abstract
Languages: RUSSIAN
Main Citation Owner: NLM
Record type: Completed
Chemical methods that accelerate the transport of insulin and other polypeptides across biological membranes and increase their resistance to enzymatic hydrolysis are reviewed. These methods include chemical **modification** of insulin macromolecules, the use of compounds that increase the permeability of biological membranes or inhibit enzymatic proteolysis, the hormone immobilization in a **polymer** coat protecting it against the aggressive environment, the incorporation of insulin into **liposomes** , etc. The advantages and drawbacks of these methods are analyzed, and promising lines of research in this field of applied biochemistry are described.

3/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09156498 97048442 PMID: 8893278
Lectin-bearing **polymerized liposomes** as potential oral vaccine carriers.
Chen H; Torchilin V; Langer R
Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge 02139, USA.
Pharmaceutical research (UNITED STATES) Sep **1996**, 13 (9)

p1378-83, ISSN 0724-8741 Journal Code: 8406521
Contract/Grant No.: GM 26698; GM; NIGMS; HD 29129; HD; NICHD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PURPOSE: The potential of using lectin-**modified polymerized liposomes** as Peyer's patch targeted oral delivery vehicles was examined. METHODS: Two types of lectins, Ulex Europaeus Agglutinin I (UEA I) and Wheat Germ Agglutinin (WGA), were **modified** with a hydrophobic anchor N-glutaryl-phosphotidylethanolamine (NGPE). The **modified** lectins were incorporated into **liposome** bilayers and the **liposomes** were subsequently stabilized through **polymerization**. The presence of the lectins on the **liposome** surfaces was first confirmed with X-ray photoelectron spectroscopy. Surface-immobilized lectins were then shown to retain their carbohydrate binding activities as well as specificities based on an in vitro aggregation assay. Finally, delivery efficiencies of lectin-bearing **liposomes** were determined in mice. RESULTS: About 10.5% UEA I **liposomes** and 5.8% WGA **liposomes** were taken up from the gastrointestinal tract. These numbers are significantly higher than the 3.2% observed in the case of lectin-free **liposomes**. At the same time, UEA I **liposomes** exhibited the most effective Peyer's patch targeting among the three, which directly correlated with the highest delivery efficiency observed. CONCLUSIONS: This establishes that lectin **modification** of **liposomes** can promote binding to Peyer's patches, which will give improved efficiency for Peyer's patch targeted delivery. All these point to the potential for these lectin-**modified liposomes** as novel vehicles for oral vaccination.

3/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09109809 97020267 PMID: 8866652
Polyethylene glycol **modification**: relevance of improved methodology to tumour targeting.
Francis G E; Delgado C; Fisher D; Malik F; Agrawal A K
Molecular Cell Pathology, Royal Free Hospital School of Medicine, London, U.K.
Journal of drug targeting (SWITZERLAND) **1996**, 3 (5) p321-40, ISSN 1061-186X Journal Code: 9312476
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Of all the **polymers** applied to molecule altering structural chemistry, polyethylene glycol (PEG) **modification** has numerous benefits and relatively few drawbacks. PEG is now increasingly being applied to the problems of tumour targeting, both in the context of the passive targeting of PEG-**liposomes** and in active targeting strategies using PEGylated anti-tumour antibodies. PEG can also serve as a useful linker molecule between targeting moieties and other agents, including cytotoxic or imaging agents and targeted **liposomes**. Despite these demonstrated benefits and the level of attention which PEGylation has received, relatively little consideration has been given to two key areas: first, the extent to which the coupling method has an impact on both the functionality of the PEG-adduct and the acquisition of beneficial properties; second, that the impact of PEGylation on biodistribution is complex, thus any attempt to optimise a PEG-peptide or PEG-**liposome** for a particular task must involve an examination of all the individual facets of the effects of PEGylation. Studies investigating the underlying principles of tumour targeting suggest that current views concerning the optimisation of PEGylated vehicles for tumour localisation need to be

re-examined.

3/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09030865 96402524 PMID: 8962949
Effect of **liposome** -albumin coatings on ferric ion retention and release from chitosan beads.
Chandy T; Sharma C P
Division of Biosurface Technology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, India.
Biomaterials (ENGLAND) Jan **1996**, 17 (1) p61-6, ISSN 0142-9612 Journal Code: 8100316
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Ferric chloride was embedded in a chitosan matrix to develop a prolonged-release form. The in vitro release profiles of ferric ions from chitosan beads were monitored in 0.1 M Tris-HCl buffer, pH 7.4, using a UV spectrophotometer. The amount of drug release was much higher initially, followed by a constant slow release profile for a prolonged period. The initial burst release was substantially **modified** with **liposome** and albumin coatings. From scanning electron microscope studies, it appears that the ferric ions diffuse out slowly to the dissolution medium through the micropores of the chitosan matrix. Further, the **liposome** forms a phospholipid membrane layer in the pores of chitosan beads and encapsulates the ferric ions within their vesicles and controls the release profile. The chitosan beads loaded with ferric ions substantially inhibited the polyurethane-associated calcification, in an in vitro model system. The released ferric ions, appeared to alter the protein-surface binding and improved the biocompatibility of the matrix. The results propose the possibility of **modifying** the **polymer** matrix to obtain a desired controlled release of the drug for a prolonged period.

3/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08897468 96263414 PMID: 8653480
Antisense strategies and therapeutic applications.
Putnam D A
Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, UT 84112, USA.
American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists (UNITED STATES) Jan 15 **1996**, 53 (2) p151-60; quiz 182-3, ISSN 1079-2082 Journal Code: 9503023
Contract/Grant No.: GM08393; GM; NIGMS
Erratum in Am J Health Syst Pharm 1996 Feb 1;53(3) 325
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The concepts underlying the antisense approach to disease therapy are discussed, and potential applications are examined. Antisense therapeutic agents bind to DNA or RNA sequences, blocking the synthesis of cellular proteins with unparalleled specificity. Transcription and translation are the two processes with which the agents interfere. There are three major classes of antisense agents: antisense sequences, commonly called antisense oligonucleotides; antigene sequences; and ribozymes. Antisense sequences are derivatives of nucleic acids that hybridize cytosolic messenger RNA (mRNA) sense strands through hydrogen bonding to complementary nucleic acid

bases. Antigene sequences hybridize double-stranded DNA in the nucleus, forming triple helixes. Ribozymes, rather than inhibiting protein synthesis simply by binding to a single targeted mRNA, combine enzymatic processes with the specificity of antisense base pairing, creating a molecule that can incapacitate multiple targeted mRNAs. Antisense therapeutic agents are being investigated in vitro and in vivo for use in treating human immunodeficiency virus infection, hepatitis B virus infection, herpes simplex virus infection, papillomavirus infection, cancer, restenosis, rheumatoid arthritis, and allergic disorders. Although many results are preliminary, some are promising and have led to clinical trials. A major goal in developing methods of delivering antisense agents is to reduce their susceptibility to nucleases while retaining their ability to bind to targeted sites. **Modification** of the phosphodiester linkages in oligonucleotides can lend the sequences enzymatic stability without affecting their binding capacities. Carrier systems designed to protect the antisense structure and improve passage through the cell membrane include **liposomes**, water-soluble **polymers** , and nanoparticles. The pharmacokinetics of antisense agents are under investigation. Antisense therapeutic agents have the potential to become an integral part of medicinal regimens.

3/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08840925 96190763 PMID: 8611610
Kinetics of membrane micellization by the hydrophobic polyelectrolyte poly(2-ethylacrylic acid).
Thomas J L; Devlin B P; Tirrell D A
Department of Polymer Science and Engineering, University of Massachusetts, Amherst 01003, USA.
Biochimica et biophysica acta (NETHERLANDS) Jan 12 **1996**, 1278 (1) p73-8, ISSN 0006-3002 Journal Code: 0217513
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Rates of pH-dependent micellization of multilamellar vesicles by the hydrophobic polyelectrolyte poly(2-ethylacrylic acid) (PEAA) have been measured turbidometrically. This **polymer** shows a strong ph-dependence in its affinity for phospholipid membranes, binding in increasing amounts as pH is lowered and ultimately solubilizing membranes to form mixed micelles (Tirrell, Takigawa and Seki (1985) Ann. N.Y. Acad. Sci. 446, 237). The rate of solubilization of dipalmitoylphosphatidylcholine (DPPC) vesicle suspensions by PEAA increases approximately linearly with reductions in pH below a threshold at pH 6.55. Interestingly, negatively-charged dipalmitoylphosphatidylglycerol membranes showed qualitatively similar behavior in the presence of PEAA, and incorporation of 10% or 20% dipalmitoylphosphatidic acid in DPPC membranes did not affect solubilization rates, demonstrating that membrane charge is not an important factor in determining micellization kinetics. Micellization of DPPC and dimyristoylphosphatidylcholine membranes occurs most rapidly at their respective gel-liquid crystalline transition temperatures (Tm); the rate enhancement is correlated with a peak in the temperature-dependent binding of a fluorescently-**modified** PEAA in slightly alkaline solutions in which no micellization is observed. The lateral compressibility of the membrane, which has a similar peak at Tm, is proposed to be an important determinant of the rate and extent of **polymer** adsorption, and consequently of the rate of micellization.

3/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

because at the same molar content of anchoring groups, each attachment point carries two **polymeric** chains and doubles the quantity of **liposome**-grafted **polymer** comparing to linear poly(ethylene glycol).

3/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08731559 96081886 PMID: 7499344
Inhibition of gene expression by triple helix formation in hepatoma cells.
Tu G C; Cao Q N; Israel Y
Department of Pathology, Anatomy and Cell Biology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania 19107, USA.
Journal of biological chemistry (UNITED STATES) Nov 24 **1995**, 270 (47) p28402-7, ISSN 0021-9258 Journal Code: 2985121R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The aim of this study was to selectively inhibit human mitochondrial aldehyde dehydrogenase (ALDH2) gene expression by triple helix assembly. Eight 21-mer oligodeoxyribonucleotides were designed to bind to two purine-rich sequences in the 5'-flanking region of the human ALDH2 gene. Gel mobility shift assays showed that triplex formation is sequence-specific for the target duplex and the third strand oligonucleotide. In the presence of Mg2+, but absence of K+, triplex-forming oligonucleotides bind to their target sites with apparent dissociation constants (Kd) in the 10(-7) to 10(-9) M range. Potassium cation virtually suppressed the triplex formation of G-C-rich duplex DNA with natural oligonucleotides, but did not prevent triplex formation with phosphorothioate-**modified** oligonucleotides. Phosphorothioate-**modified** oligonucleotides were delivered into human hepatoma Hep G2 cells by cationic **liposomes**. The reduction in ALDH2 mRNA levels in the cells was determined by the competitive reverse transcription-**polymerase** chain reaction. One of the phosphorothioate-**modified** oligonucleotides designed to forma an antiparallel triplex with a target in the 5'-flanking region of human ALDH2 gene (-105 to -125 from the translation initiation codon ATG) reduced by 80-90% the ALDH2 mRNA levels without affecting albumin mRNA levels. Data suggest that triple-helix formation may provide a means to selectively inhibit hepatic ALDH2 gene expression for therapeutic use.

3/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08711029 96050501 PMID: 10155705
The development of hemoglobin solutions as red cell substitutes: hemoglobin solutions.
Gould S A; Sehgal L R; Sehgal H L; Moss G S
Department of Surgery, Michael Reese Hospital and Medical Center, Chicago University of Illinois, College of Medicine 60201, USA.
Transfusion science (ENGLAND) Mar **1995**, 16 (1) p5-17, ISSN 0955-3886 Journal Code: 9001514
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Although the efficacy of hemoglobin-based oxygen carriers was established more than 60 years ago, all prior clinical trials have demonstrated significant toxicity characterized by renal dysfunction, gastrointestinal

distress, and systemic vasoconstriction. The mechanisms of these toxicities now appear to be understood. Tetrameric forms of the hemoglobin molecule extravasate from the circulation and interact with endothelial derived relaxing factor, leading to unopposed vasoconstriction. Although numerous efforts are underway to chemically **modify** the native tetramer, it is likely that all tetrameric forms of the hemoglobin molecule will continue to extravasate. We have focused on developing a **polymerized** form of hemoglobin that is virtually free of unreacted tetramer. The development and characterization of this **polymerized** pyridoxylated hemoglobin solution (Poly SFH-P) is described. Clinical trials have been completed successfully in volunteers, and are now underway to assess the safety and efficacy of Poly SFH-P as a clinically useful red cell substitute in the treatment of acute blood loss in the setting of trauma and surgery.

3/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08669008 96014955 PMID: 7576316
Encapsulation of foscarnet in **liposomes modifies** drug intracellular accumulation, in vitro anti-HIV-1 activity, tissue distribution and pharmacokinetics.
Dusserre N; Lessard C; Paquette N; Perron S; Poulin L; Tremblay M; Beauchamp D; Desormeaux A; Bergeron M G
Centre de Recherche en Infectiologie, Centre Hospitalier de I'Universite Laval, Ste-Foy, Quebec, Canada.
AIDS (London, England) (UNITED STATES) Aug **1995**, 9 (8) p833-41
, ISSN 0269-9370 Journal Code: 8710219
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
OBJECTIVE: To improve the in vitro anti-HIV-1 activity, intracellular accumulation in macrophages and in vivo pharmacokinetics and tissue distribution of foscarnet (trisodium phosphonoformate; PFA) by encapsulation in **liposomes**. METHODS: The accumulation of free and **liposome** -encapsulated PFA was determined in monocyte-macrophage RAW 264.7 cells and human premonocytoid U937 cells. The antiviral activity was evaluated in U937 cells infected with HIV-1IIIB. Tissue distribution and pharmacokinetics of free and liposomal PFA were determined in female Sprague-Dawley rats following the administration of an intravenous bolus dose (10 mg PFA/kg). RESULTS: The entrapment of PFA in **liposomes** resulted in a higher drug accumulation in both U937 and RAW 264.7 cells. A slightly greater efficacy against HIV-1IIIB replication into U937 cells was observed upon encapsulation of PFA into **liposomes** . Improved pharmacokinetics was observed upon entrapment of PFA in **liposomes**. Much higher drug levels were found in plasma for the liposomal formulation. The systemic clearance of the liposomal drug was 77 times lower than that of free drug. The encapsulation of PFA in **liposomes** greatly enhanced the drug accumulation in organs of the reticuloendothelial system. CONCLUSION: The encapsulation of PFA in **liposomes modified** the tissue distribution and plasma pharmacokinetics of the antiviral agent, resulting in a marked improvement of drug accumulation in organs involved in HIV immunopathogenesis and in a greater PFA bioavailability. The antiviral activity of liposomal PFA was slightly greater than that of free drug in HIV-1IIIB-infected U937 cells.

3/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08577590 95337321 PMID: 7612834
Range and magnitude of the steric pressure between bilayers containing phospholipids with covalently attached poly(ethylene glycol).

Kenworthy A K; Hristova K; Needham D; McIntosh T J
Department of Cell Biology, Duke University Medical Center, Durham, North Carolina 27710, USA.
Biophysical journal (UNITED STATES) May **1995**, 68 (5) p1921-36, ISSN 0006-3495 Journal Code: 0370626
Contract/Grant No.: GM-27278; GM; NIGMS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The interactive properties of **liposomes** containing phospholipids with covalently attached poly(ethylene glycol) (PEG-lipids) are of interest because such **liposomes** are being developed as drug delivery vehicles and also are ideal model systems for measuring the properties of surface-grafted **polymers**. For bilayers containing PEG-lipids with PEG molecular weights of 350, 750, 2000, and 5000, pressure-distance relations have been measured by X-ray diffraction analysis of **liposomes** subjected to known applied osmotic pressures. The distance between apposing bilayers decreased monotonically with increasing applied pressure for each concentration of a given PEG-lipid. Although for bilayers containing PEG-350 and PEG-750 the contribution of electrostatic repulsion to interbilayer interactions was significant, for bilayers containing PEG-2000 and PEG-5000 the major repulsive pressure between bilayers was a steric pressure due to the attached PEG. The range and magnitude of this steric pressure increased both with increasing PEG-lipid concentration and PEG size, and the extension length of the PEG from the bilayer surface at maximum PEG-lipid concentration depended strongly on the size of the PEG, being less than 35 A for PEG-750, and about 65 A for PEG-2000 and 115 A for PEG-5000. The measured pressure-distance relations have been modeled in terms of current theories (deGennes, 1987; Milner et al., 1988b) for the steric pressure produced by surface-grafted **polymers**, as **modified** by us to take into account the effects of **polymer** polydispersity and the possibility that, at low grafting densities, **polymers** from apposing bilayers surfaces can interpenetrate or interdigitate. No one theoretical scheme is sufficient to account for all the experimental results. However, for a given pressure regime, PEG-lipid size, and PEG-lipid surface density, the appropriately **modified** theoretical treatment gives a reasonable fit to the pressure-distance data.

3/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08557221 95313951 PMID: 7793636
Phospholipid/alkanethiol bilayers for cell-surface receptor studies by surface plasmon resonance.
Plant A L; Brigham-Burke M; Petrella E C; O'Shannessy D J
Biotechnology Division, National Institute of Standards and Technology, Gaithersburg, Maryland 20899, USA.
Analytical biochemistry (UNITED STATES) Apr 10 **1995**, 226 (2) p342-8, ISSN 0003-2697 Journal Code: 0370535
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Supported hybrid bilayer membranes (HBM) composed of a monolayer of phospholipid and a monolayer of alkanethiol associated with a thin gold film on glass are useful as model lipid bilayer membranes for studying membrane receptor-ligand and cell-cell binding events by surface plasmon resonance (SPR). Measurements of specific binding of proteins and lipid vesicles to well-defined HBMs have been performed under conditions of continuous flow using a commercial SPR instrument (BIAcore). HBMs are shown to be stable in flow and to block nonspecific adsorption of proteins to the alkanethiol/gold surface. The use of such supported lipid bilayers in flow

provides a means of conducting equilibrium and kinetic studies of models of ligand-cell and cell-cell interactions with receptors or ligands in a membrane environment. Compared to the extended dextran **polymer** layer that is currently used for surface **modification** of BIAcore "sensor chips," the described HBMs provide a well-defined surface that will permit less ambiguous modeling of these important biological interactions.

3/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08548625 95308703 PMID: 7540514
Ribozyme-mediated inhibition of expression of leukocyte-type 12-lipoxygenase in porcine aortic vascular smooth muscle cells.
Gu J L; Veerapanane D; Rossi J; Natarajan R; Thomas L; Nadler J
Department of Diabetes, Endocrinology, and Metabolism, City of Hope Medical Center, Duarte, CA 91010, USA.
Circulation research (UNITED STATES) Jul **1995**, 77 (1) p14-20, ISSN 0009-7330 Journal Code: 0047103
Contract/Grant No.: R01-DK-39721; DK; NIDDK; R29-HL-48920; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Activation of a leukocyte-type 12-lipoxygenase (12-LO) has been proposed to be an important mechanism for angiotensin II- and glucose-induced vascular smooth muscle cell growth. Currently, no specific pharmacological inhibitors for the leukocyte-type 12-LO are available to test this hypothesis. We have therefore designed a chimeric DNA-RNA hammerhead ribozyme to produce cleavage at the first GUC sequence at nucleotide 7 of porcine leukocyte 12-LO mRNA. The ribozyme was tested in vitro with a 206-base 12-LO mRNA as substrate. We observed that the ribozyme specifically and dose-dependently cleaved porcine leukocyte 12-LO mRNA at the predicted site under physiological temperature. Furthermore, we also efficiently delivered the ribozyme into porcine aortic vascular smooth muscle cells by transfection with cationic **liposomes**. The ribozyme caused a dose-dependent decrease in levels of porcine leukocyte-type 12-LO mRNA in these cells and was more potent than an antisense oligonucleotide directed against porcine leukocyte 12-LO. The 12-LO ribozyme also attenuated 12-LO protein levels in the cells. The action of the ribozyme was primarily a result of its catalytic activity, since a **modified** ribozyme that lacks catalytic activity showed reduced effects. This represents the first ribozyme directed against a mammalian LO pathway. These results demonstrate the potential utility of new ribozyme technology to generate novel agents for gene modulation experiments to **modify** the development or progression of vascular disease in humans.

3/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08461241 95219335 PMID: 7704484
Sterically stabilized **liposomes** : physical and biological properties.
Woodle M C; Newman M S; Cohen J A
Liposome Technology, Inc., Menlo Park, CA 94025.
Journal of drug targeting (SWITZERLAND) **1994**, 2 (5) p397-403, ISSN 1061-186X Journal Code: 9312476
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Advanced liposomal therapeutics has been attained by **liposome** surface **modification** , initially with specific glycolipids and

subsequently with surface-grafted PEG, reducing in vivo rapid recognition and uptake, giving prolonged blood circulation, and providing selective localization in tumors and other pathological sites, as described in recent reviews. The result is improved efficacy of encapsulated agents. The surface PEG may produce a steric barrier, as described for colloids. Reduced in vivo uptake may result from inhibition of plasma-protein adsorption, or opsonization, by the steric coating. Several physical studies support this mechanism, including electrophoretic mobility (zeta potential). Our previous results for 2000-dalton PEG indicated a coating thickness about 5 nm, in agreement with independent measurements. We report here results for 750 to 5000-dalton PEGs. The calculated coating thickness increases with molecular weight in a nonlinear fashion. The dependence of blood circulation and tissue distribution on PEG molecular weight correlates with zeta-potential estimates of PEG-coating thickness. Effects on tissue distribution are reported for liver and spleen, the major phagocytic organs. The biological properties of these **liposomes** depend on the surface **polymer** rather than the lipid bilayer, yielding important advantages for lipid-mediated control of drug interaction and release without affecting the biodistribution.

3/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08454712 95209097 PMID: 7695075
Modified hemoglobins as oxygen transporting blood substitutes]
Hamoglobinmodifikationen als sauerstofftransportierende Blutersatzmittel.
Waschke K F
Institut fur Anasthesiologie und Operative Intensivmedizine, Fakultat fur Klinische Medizin Mannheim, Universitat Heidelberg.
Der Anaesthesist (GERMANY) Jan **1995**, 44 (1) p1-12, ISSN 0003-2417 Journal Code: 0370525
Document type: Journal Article; Review; Review, Tutorial ; English Abstract
Languages: GERMAN
Main Citation Owner: NLM
Record type: Completed
Although the attempts to develop an oxygen-carrying alternative to red blood cells (RBC) have spanned the last 100 years, it has proven difficult to develop a clinically useful haemoglobin-based oxygen carrier. Four major problems have been shown to compromise the use of haemoglobin outside the RBC as an oxygen carrier: (1) the increased oxygen affinity due to the loss of 2,3-diphosphoglycerate; (2) dissociation into dimers and monomers with consequent renal and capillary loss of hemoglobin; (3) insufficient concentrations of prepared solutions under iso-oncotic conditions, and thereby reduced oxygen-carrying capacity; and (4) toxicity. Most of these limitations have been overcome by different **modifications** of haemoglobin, including pyridoxylation, intra- and intermolecular cross-linking, **polymerisation**, **liposome** encapsulation, conjugation to inert macromolecules, and genetic engineering. Questions of toxicity are not completely answered at present, especially with regard to renal toxicity, interactions with the nitric oxide system, and antigenicity. Therefore, the issues preventing clinical application are those of safety and not of efficacy of haemoglobin-based RBC substitutes. Potential clinical applications include fluid resuscitation, treatment of anaemia and ischaemia, support in extracorporeal circulation, and organ preservation. Based on promising and reproducible results obtained from animal studies, clinical phase I and II trials with newer haemoglobin solutions have been started in the United States. Substantial knowledge has been gained in the development, production, and evaluation of haemoglobin-based oxygen carriers during the past years. It will probably not take another century before oxygen-carrying RBC substitutes will become available for clinical use.

3/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08412817 95178599 PMID: 7873652
New amphipatic **polymer**-lipid conjugates forming long-circulating reticuloendothelial system-evading **liposomes**.
Woodle M C; Engbers C M; Zalipsky S
Liposome Technology, Inc., Menlo Park, California 94025.
Bioconjugate chemistry (UNITED STATES) Nov-Dec **1994**, 5 (6) p493-6, ISSN 1043-1802 Journal Code: 9010319
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Lipid-conjugates of two amphipatic **polymers**, poly(2-methyl-2-oxazoline) (PMOZ) and poly(2-ethyl-2-oxazoline) (PEOZ) (degree of **polymerization** approximately 50) were synthesized by linking glutarate esters of the **polymers** to distearoylphosphatidylethanolamine (DSPE) or alternatively by termination of the **polymerization** process with DSPE. Surface-**modified** **liposomes** (90 +/- 5 nm) prepared from either conjugate (5 mol % of total lipid) were injected into rats and followed by blood level and tissue distribution measurements. Both **polymers** PEOZ and PMOZ were found to convey long circulation and low hepatosplenic uptake to **liposomes** to the same extent as polyethylene glycol (PEG), the best known material for this purpose. This is the first demonstration of protection from rapid recognition and clearance conveyed by alternative **polymers**, which is equal to the effect of PEG.

3/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08393114 95134363 PMID: 7832999
The surface properties of phospholipid **liposome** systems and their characterisation.
Jones M N
School of Biological Sciences, University of Manchester, UK.
Advances in colloid and interface science (NETHERLANDS) Jan 3 **1995**, 54 p93-128, ISSN 0001-8686 Journal Code: 8706645
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The field of **liposome** (vesicle) research has expanded considerably over the last 30 years. In physical chemical terms **liposomes** have many of the characteristics of colloidal particles and their stability is determined in part by the classical surface forces. It is now possible to engineer a wide range of **liposomes** varying in size, phospholipid composition and surface characteristics. The surfaces of **liposomes** can be **modified** by the choice of bilayer lipid as well as by the incorporation and covalent linkage of proteins (e.g. antibodies and sugar binding proteins [lectins]), glycoproteins and synthetic **polymers**. Much of the impetus for **liposome** design has come from their potential value as drug delivery systems. The development of technologies for the production of such a range of **liposome** systems has presented interesting problems in the characterisation of their properties. The review addresses the progress that has been made in characterising the surfaces of different types of **liposomes** with specific reference to their electrophoretic properties and their interpretation and the physical interactions between liposomal bilayers.

3/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08366031 95113834 PMID: 7814384
A structure-function study of bovine pancreatic phospholipase A2 using **polymerized** mixed **liposomes**.
Dua R; Wu S K; Cho W
Department of Chemistry, University of Illinois, Chicago 60607-7061.
Journal of biological chemistry (UNITED STATES) Jan 6 **1995**, 270 (1) p263-8, ISSN 0021-9258 Journal Code: 2985121R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A new combinatorial approach that includes the genetic variation of protein structure and the chemical **modification** of phospholipid structure in **polymerized** mixed **liposomes** was used to delineate the structure-function relationships in the interfacial catalysis of bovine pancreatic phospholipase A2 (PLA2). Based on previous structural and mutational studies, several bovine PLA2 mutants were generated in which a positive charge of putatively important lysyl side chains was reversed (K10E, K53E, K56E, and K116E) or neutralized (K56Q and K116Q). Kinetic parameters of bovine wild type and mutant PLA2s determined using **polymerized** mixed **liposomes** consisting of 1-hexadecanoyl-2-(1-p yrenedecanoyl)-sn-glycero-3-phosphoethanolamine (or -phosphoglycerol) and 1,2-bis[12-(lipoyloxy)dodecanoyl]-sn-glycero-3-phosphoglycerol showed that Lys-53 is involved specifically in the interaction with a substrate bound in the active site. Also, these results showed that Lys-10 and Lys-116 are involved in the interaction of bovine PLA2 with anionic interfaces but not in the interaction with the active site-bound substrate. In particular, Lys-116 makes more significant contribution than Lys-10 by approximately 1.0 kcal/mol to the binding to anionic interfaces. Most importantly, Lys-56 was shown to participate in the interaction with both the active site-bound substrate and anionic interfaces. These findings establish Lys-56 and Lys-116 as essential residues for the binding of bovine pancreatic PLA2 to anionic interfaces. Lastly, our structure-function analysis based on the use of **polymerized** mixed **liposomes** was further supported by equilibrium binding measurements of these proteins using 1,2-bis[12-(lipoyloxy)dodecanoyl]-sn-glycero-3-phosphoglycerol **polymeriz ed liposomes** and by kinetic analyses using monomeric substrates, 1,2-dihexanoyl-sn-glycero-3-phosphoethanolamine and -phosphoglycerol.

3/3,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08334540 95094014 PMID: 8000899
Drug delivery systems for the future.
Hnatyszyn H J; Kossovsky N; Gelman A; Sponsler E
Department of Pathology and Laboratory Medicine, University of California, Los Angeles School of Medicine.
PDA journal of pharmaceutical science and technology / PDA (UNITED STATES) Sep-Oct **1994**, 48 (5) p247-54, ISSN 1079-7440 Journal Code: 9439538
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Parenteral drug delivery systems have the potential to make drugs both safer and more effective. While research in this field has been active for over 30 years, the current fiscal constraints of health care delivery add a greater degree of urgency to finding a working system. The three competing technologies currently under development include prodrug or zymogen-like systems, simple soluble macromolecular systems, and complex particulate

multicomponent systems. In this review, the advantages, disadvantages, and areas for further development of these three basic technology systems are compared and contrasted; the biophysical constraints are considered; and a model solution system using surface **modified** nanocrystalline ceramics is described.

3/3,AB/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08241832 95002072 PMID: 7918561
Amphiphilic vinyl **polymers** effectively prolong **liposome** circulation time in vivo.
Torchilin V P; Shtilman M I; Trubetskoy V S; Whiteman K; Milstein A M
Center for Imaging and Pharmaceutical Research, Massachusetts General Hospital-East, Charlestown 02129.
Biochimica et biophysica acta (NETHERLANDS) Oct 12 **1994**, 1195 (1) p181-4, ISSN 0006-3002 Journal Code: 0217513
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Newly synthesized amphiphilic polyacrylamide and poly(vinyl pyrrolidone), single terminus-**modified** with long-chain fatty acyl groups, are able to incorporate into the liposomal membrane, and similar to poly(ethylene glycol) prolong **liposome** circulation in vivo and decrease **liposome** accumulation in the liver. Protective efficacy of **modified polymers** increases with the increase in the length of acyl moiety and decreases for higher molecular weight **polymers**. The data on amphiphilic **polymer-modified liposome** biodistribution are presented.

3/3,AB/24 (Item 24 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08241822 95002062 PMID: 7918551
Poly(ethylene glycol) on the **liposome** surface: on the mechanism of **polymer**-coated **liposome** longevity.
Torchilin V P; Omelyanenko V G; Papisov M I; Bogdanov A A; Trubetskoy V S; Herron J N; Gentry C A
Center for Imaging and Pharmaceutical Research, Massachusetts General Hospital-East, Charlestown 02129.
Biochimica et biophysica acta (NETHERLANDS) Oct 12 **1994**, 1195 (1) p11-20, ISSN 0006-3002 Journal Code: 0217513
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The hypothetical model is built explaining the molecular mechanism of protective action of poly(ethylene glycol) on **liposomes** in vivo. The protective layer of the **polymer** on the **liposome** surface is considered as a statistical 'cloud' of **polymer** possible conformations in solution. Computer simulation was used to demonstrate that relatively a small number of **liposome** -grafted molecules of hydrophilic and flexible **polymer** can create a dense protective conformational cloud over the **liposome** surface preventing opsonizing protein molecules from contacting **liposome**. A more rigid **polymer** fails to form this dense protective cloud, even when hydrophilic. Computer simulation was also used to reveal possible heterogeneity of reactive sites on a **polymer**-coated **liposome** surface, and to estimate the optimal **polymer**-to-lipid ratio for efficient **liposome** protection. Experiments have been performed with the quenching of **liposome** -associated fluorescent label (nitrobenzoxadiazole or fluorescein) with

protein (rhodamine-ovalbumin or anti-fluorescein antibody) from solution. It was shown that poly(ethylene glycol) grafting to **liposomes** hinders protein interaction with the **liposome** surface, whereas **liposome** -grafted dextran (more rigid **polymer**) in similar quantities does not affect protein-**liposome** interaction. Highly-reactive and low-reactive populations of chemically identical reactive sites have been found on **polymer**-coated **liposomes** . Experimental data satisfactory confirm the suggested mechanism for the longevity of **polymer-modified liposome**.

3/3,AB/25 (Item 25 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08204072 94339347 PMID: 8061197
Modulation of interaction forces between bilayers exposing short-chained ethylene oxide headgroups.
Kuhl T L; Leckband D E; Lasic D D; Israelachvili J N
Department of Chemical and Nuclear Engineering, University of California, Santa Barbara 93106.
Biophysical journal (UNITED STATES) May **1994**, 66 (5) p1479-88, ISSN 0006-3495 Journal Code: 0370626
Contract/Grant No.: GM47334; GM; NIGMS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The use of **liposomes** as drug delivery systems has been limited by their rapid clearance from circulation by the mononuclear phagocyte system. Recent studies have found that circulation times can be greatly enhanced by incorporating a small amount of **modified** lipids whose headgroups are derivatized with a bulky water soluble **polymeric** chain of poly ethylene oxide. We report here a systematic study using the Surface Forces Apparatus to measure directly the interactions between two phosphatidyl ethanolamine lipid bilayers, exposing this **polymeric** headgroup at different concentrations in the bilayer. We found that the force becomes repulsive at all separations and that the thickness of the steric barrier could be controlled easily by adjusting the concentration of the **modified** lipids. Equilibrium force profiles were measured that were reversible and largely insensitive to changes in electrolyte concentration and temperature. The results have enabled the Dolan and Edwards theory for the steric forces of low coverage **polymer** surfaces and the Alexander de Gennes theory for high coverage surfaces to be tested, and both were found to apply. We conclude that these simple theories can be used to model the interactions of surprisingly short segments and, hence, apply to such systems as lipids with bulky headgroups and **liposomes** containing a sterically stabilizing **polymer**.

3/3,AB/26 (Item 26 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07963340 94100242 PMID: 8274504
Interactions of **liposomes** and hydrophobically-**modified** poly-(N-isopropylacrylamides): an attempt to model the cytoskeleton.
Ringsdorf H; Sackmann E; Simon J; Winnik F M
Institut fur Organische Chemie, Johannes Gutenberg-Universitat Mainz, Germany.
Biochimica et biophysica acta (NETHERLANDS) Dec 12 **1993**, 1153 (2) p335-44, ISSN 0006-3002 Journal Code: 0217513
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The interactions of small unilamellar vesicles (SUV) and water-soluble copolymers were studied by fluorescence spectroscopy, differential scanning calorimetry (DSC) and quasi-elastic light scattering (QELS). The anchoring onto liposomal bilayer membranes of copolymers of N-isopropylacrylamide, N-(2-(1-naphthyl)ethyl)-N-n-octadecylacrylamide and or N-[4-(1-pyrenyl)butyl]-N-n-octadecylacrylamide (0.5 mol% of the octadecylacrylamide comonomer) was monitored by non-radiative energy transfer between excited naphthalene and pyrene. The anchoring process occurred on zwitterionic lecithin **liposomes** and on negatively charged phosphatidic acid **liposomes**, whether the bilayer was in the crystalline or the liquid-crystalline phase. Insertion of the copolymer octadecyl groups within crystalline bilayers was attributed to the presence of packing defects. Aqueous solutions of poly-(N-isopropylacrylamide) and of its hydrophobically-**modified** copolymers exhibit a lower critical solution temperature (LCST). The coil to globule collapse of the **polymer** chains which is known to occur as the aqueous solution is heated through the LCST, also took place when the copolymers were anchored onto vesicular bilayers. The copolymers remained anchored during this collapse and the **liposomes** were not destroyed. The process was thermo-reversible. Detailed aspects of the reversibility of the phenomenon depended on the relative values of the phase transition temperatures of the **liposomes** and of the **polymer** LCST.

3/3,AB/27 (Item 27 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07933293 94068592 PMID: 8248244

Direct gene transfer with DNA-**liposome** complexes in melanoma: expression, biologic activity, and lack of toxicity in humans.

Nabel G J; Nabel E G; Yang Z Y; Fox B A; Plautz G E; Gao X; Huang L; Shu S; Gordon D; Chang A E

Howard Hughes Medical Institute, Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor 48109-0650.

Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Dec 1 **1993**, 90 (23) p11307-11, ISSN 0027-8424 Journal Code: 7505876

Contract/Grant No.: AI129179; AI; NIAID; P01 CA59327; CA; NCI; U01-AI33355; AI; NIAID; +

Document type: Clinical Trial; Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Direct gene transfer offers the potential to introduce DNA encoding therapeutic proteins to treat human disease. Previously, gene transfer in humans has been achieved by a cell-mediated ex vivo approach in which cells from the blood or tissue of patients are genetically **modified** in the laboratory and subsequently returned to the patient. To determine the feasibility and safety of directly transferring genes into humans, a clinical study was performed. The gene encoding a foreign major histocompatibility complex protein, HLA-B7, was introduced into HLA-B7-negative patients with advanced melanoma by injection of DNA-**liposome** complexes in an effort to demonstrate gene transfer, document recombinant gene expression, and determine the safety and potential toxicity of this therapy. Six courses of treatment were completed without complications in five HLA-B7-negative patients with stage IV melanoma. Plasmid DNA was detected within biopsies of treated tumor nodules 3-7 days after injection but was not found in the serum at any time by using the **polymerase** chain reaction. Recombinant HLA-B7 protein was demonstrated in tumor biopsy tissue in all five patients by immunochemistry, and immune responses to HLA-B7 and autologous tumors could be detected. No antibodies to DNA were detected in any patient. One patient demonstrated regression of injected nodules on two independent treatments, which was accompanied by regression at distant sites. These studies

demonstrate the feasibility, safety, and therapeutic potential of direct gene transfer in humans.

3/3,AB/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07834513 93364269 PMID: 8358299
Refolding and proton pumping activity of a polyethylene glycol-bacteriorhodopsin water-soluble conjugate.
Sirokman G; Fasman G D
Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02254-9110.
Protein science : a publication of the Protein Society (UNITED STATES) Jul **1993**, 2 (7) p1161-70, ISSN 0961-8368 Journal Code: 9211750
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Bacteriorhodopsin (BR), from the purple membrane (PM) of Halobacterium halobium, was chemically **modified** with methoxypolyethylene glycol (m-PEG; molecular weight = 5,000 Da) succinimidyl carbonate. The polyethylene glycol-bacteriorhodopsin (m-PEG-SC-BR33) conjugate, containing one polyethylene glycol chain, was water soluble. The secondary structure of the conjugate in water appeared partially denatured, but was shown to contain alpha-helical segments by circular dichroism spectroscopy. The isolated bacteriorhodopsin conjugate, with added retinal, was refolded in a mixed detergent-lipid micelle and had an absorption maximum at 555 nm. The refolded conjugate was transferred into vesicles that pumped protons, upon illumination, as efficiently as did native BR. **Modification** of the PM with m-PEG did not alter the native structure or inhibit proton pumping, and therefore it is suggested that the glycol **polymer** is present as a moiety covalently linked to residues unnecessary for proton pumping and proper folding. The site of attachment of m-PEG was determined to be at either Lys 129 or Lys 159, with position Lys 129 the most probable site of attachment. The m-PEG-SC-BR33 could be stepwise refolded to the native conformation by the addition of trifluoroethanol to lower the dielectric constant, simulating the insertion of the BR into the phospholipid bilayer.

3/3,AB/29 (Item 29 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07780585 93305706 PMID: 8318529
Specific targeting with poly(ethylene glycol)-**modified** **liposomes**: coupling of homing devices to the ends of the **polymeric** chains combines effective target binding with long circulation times.
Blume G; Cevc G; Crommelin M D; Bakker-Woudenberg I A; Kluft C; Storm G
Urologische Klinik und Poliklinik, Technischen Universitat Munchen, Germany.
Biochimica et biophysica acta (NETHERLANDS) Jun 18 **1993**, 1149 (1) p180-4, ISSN 0006-3002 Journal Code: 0217513
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
One possibility for bringing drugs to their specific targets is to use the drug-laden **liposomes** that have been made target-specific by the attachment of appropriate proteins. Such 'directed' proteoliposomes and most other particles are rapidly removed from the bloodstream, however, by the mononuclear phagocytes in the liver and spleen. This causes suboptimal drug accumulation at the target site. Coating the **liposome** surface with poly(ethylene glycol) (PEG) may prolong the circulation time of

liposomes . Using plasminogen as a homing device we have shown that the PEG-**modified liposomes** with such a homing device coupled to the ends of the long PEG chains may combine long vesicle circulation times in the blood with high target binding capability. The PEG-coated proteoliposomes with homing devices attached at the very bilayer surface, on the contrary, are longlived but have only little or no capability to bind to their targets.

3/3,AB/30 (Item 30 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07624361 93152704 PMID: 1493192
Biocompatibility of lipid microcylinders: effect on cell growth and antigen presentation in culture.
Rudolph A S; Stilwell G; Cliff R O; Kahn B; Spargo B J; Rollwagen F; Monroy R L
Center for Biomolecular Science and Engineering, Naval Research Laboratory, Washington, DC 20375-5000.
Biomaterials (ENGLAND) **1992**, 13 (15) p1085-92, ISSN 0142-9612 Journal Code: 8100316
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The authors are developing a lipid-based microcylinder for the controlled release of biological response **modifiers** and as templates for cellular migration and differentiation. These structures are comprised of a photopolymerizable phosphatidylcholine (1,2-ditricosa-10,12-diynoyl-sn-glycero-3-phosphocholine) and form spontaneously as a result of a thermotropic phase transition in aqueous solution or in a cosolvent solution of 70:30 ethanol:water. The hollow cylinders are helically wrapped lipid bilayers, variable in length (50-250 microns, depending on conditions of formation) and are 0.5-1.0 microns in diameter. The interaction has been examined of three types of lipid microcylinders: (1) monomeric, (2) photopolymerized by exposure to 254 nm light, and (3) surface-**modified** by incorporation of 6 mol% gangliosides, with different human cell lines and peripheral blood leucocytes to evaluate the biocompatibility of these structures. The proliferative status of U937 (a histiocytic monocyte), K562 (an erythroleukaemic cell), and Jurkat's derivative (a T-lymphoblast) as measured by pulsed tritiated thymidine was unaffected by the presence of up to 100 micrograms/ml of lipid microcylinders after 3 d in culture. Adherent human peripheral blood monocytes were shown to form adhesive contacts with the lipid microcylinders. An 'association' index from this interaction shows that after 3 d in culture, the association was much lower for those microcylinders that had incorporated ganglioside compared with monomeric or **polymerized** structures. The lipid microcylinders do not activate T-cells isolated from human peripheral blood, nor do they inhibit the activation of T-cells by phorbol esters or other mitogens.(ABSTRACT TRUNCATED AT 250 WORDS)

3/3,AB/31 (Item 31 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07503833 93028133 PMID: 1409394
Evaluation of mucoadhesive **polymers** in ocular drug delivery. II. **Polymer**-coated vesicles.
Davies N M; Farr S J; Hadgraft J; Kellaway I W
Welsh School of Pharmacy, University of Wales, College of Cardiff, U.K.
Pharmaceutical research (UNITED STATES) Sep **1992**, 9 (9) p1137-44, ISSN 0724-8741 Journal Code: 8406521
Document type: Journal Article
Languages: ENGLISH

Main Citation Owner: NLM
Record type: Completed
Association of Carbopol 934P and Carbopol 1342 (a hydrophobic **modified** Carbopol resin) with phospholipid vesicles was assessed by photon correlation spectroscopy and microelectrophoresis at pH 7.4 and 5. The precorneal clearance of the **polymer**-coated vesicles was compared to that of uncoated vesicles by lacrimal dacryoscintigraphy in the rabbit. The mucoadhesive **polymer**-coated vesicles demonstrated significantly enhanced precorneal retention compared to noncoated vesicles only at pH 5 (P less than 0.005). The entrapment and subsequent release of tropicamide from Carbopol 1342-coated and uncoated **liposomes** were determined in vitro together with an in vivo evaluation of the vesicles formulated at the lower pH. Mucoadhesive **polymer** -coated vesicles failed to increase significantly the bioavailability of the entrapped tropicamide compared to uncoated vesicles and aqueous solution.

3/3,AB/32 (Item 32 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07463959 92399476 PMID: 1381964
Enhanced intracellular stability of dextran-horse radish peroxidase conjugate: an approach to enzyme replacement therapy.
Mumtaz S; Bachhawat B K
Department of Biochemistry, University of Delhi, India.
Biochimica et biophysica acta (NETHERLANDS) Sep 15 **1992**, 1117 (2) p174-8, ISSN 0006-3002 Journal Code: 0217513
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Horse radish peroxidase (HRP), a mannose-containing glycoprotein was covalently **modified** by conjugation with dextran. The rapid uptake of HRP by the liver is markedly inhibited by mannan. The uptake of dextran-HRP conjugate by the liver, though lower compared to that of the free enzyme, is also partially inhibited by mannan. **Liposomes** were therefore used as carriers for delivering the free and the **modified** HRP to the liver. The dextran-HRP conjugate showed greater stability intracellularly as compared to the free enzyme. The enhanced stability of enzymes upon their extensive glycosylation with nondegradable sugar **polymers** would be of importance in extending the catalytic life of therapeutically active enzymes and thereby improve their therapeutic potential for the treatment of certain enzyme deficiency disorders.

3/3,AB/33 (Item 33 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07294504 92239624 PMID: 1810407
Preparation and surface characterization of carboxymethylchitin-incorporated submicron bilayer-lipid membrane artificial cells (**liposomes**) encapsulating hemoglobin.
Mobed M; Chang T M
Artificial Cells and Organs Research Centre, McGill University, Montreal, Canada.
Biomaterials, artificial cells, and immobilization biotechnology : official journal of the International Society for Artificial Cells and Immobilization Biotechnology (UNITED STATES) **1991**, 19 (4) p731-44, ISSN 1055-7172 Journal Code: 9111988
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In view of the desirability to increase the survival time of the

lipsome-based artificial red blood cells in vivo, bovine hemoglobin-loaded **liposomes** (LEHb) are incorporated with a polyanionic **polymer**, a highly substituted type of carboxymethylchitin (CMC). The **liposomes** are prepared by a **modified** Reverse Phase Evaporation technique and then purified using a Sepharose 4B column. A comparative study between experimental techniques for the determination of adsorption efficiency suggests that FT-IR spectroscopy gives a more accurate quantitative adsorption index while the chitinase-based enzymatic assay should be used as a qualitative detection tool. The overall composition of the bilayer(s) can be approximated by that of the natural (RBC) membrane in terms of total lipids and carbohydrates at 87.8% (phospholipids and cholesterol) and 12.2% CMC respectively.

3/3,AB/34 (Item 34 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07273127 92198013 PMID: 1312805
Detergents affect insulin binding, tyrosine kinase activity and oligomeric structure of partially purified insulin receptors.
Leray V; Hubert P; Cremel G; Staedel C
INSERM U.338, Centre de Neurochimie, Strasbourg, France.
Archives of biochemistry and biophysics (UNITED STATES) Apr **1992**, 294 (1) p22-9, ISSN 0003-9861 Journal Code: 0372430
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Insulin receptor activities, i.e., insulin binding and tyrosine kinase activation depend on the lipid environment of the receptor. As detergent may disrupt or interfere with this environment, we investigated the effect of various common detergents on insulin receptor properties. Experiments were carried out (i) on solubilized and partially purified insulin receptor and (ii) on the receptor reconstituted into phosphatidylcholine vesicles. The detergents tested, Triton X-100, octyl-beta-D-glucopyranoside, octyl-beta-D-thioglucopyranoside, 3[(3-cholamidopropyl)dimethylammonio]propanesulfonic acid (Chaps), and Na deoxycholate affected the insulin receptor properties differently when compared with the control receptor in the absence of detergent. On the partially purified insulin receptor, Na deoxycholate inhibited both insulin receptor activities; octyl-beta-D-glucopyranoside and octyl-beta-D-thioglucopyranoside decreased insulin binding and kinase activation as their concentration increased, particularly above their respective critical micellar concentration (CMC). Triton X-100 was the only detergent which allowed an increase of insulin binding and kinase activation throughout the whole range of concentrations assayed. Reconstitution of the receptor into phosphatidylcholine vesicles protected the receptor from the direct effects of the detergents, for both the stimulation observed with Triton X-100 and the inhibition produced by the other detergents. In order to determine the effect of detergents on the oligomeric forms of the soluble insulin receptor, we investigated a new rapid sucrose gradient centrifugation technique. Insulin receptors were detected on the gradient by 125I insulin binding. For low concentrations of detergent, i.e., near the CMC, octylglucoside, Chaps, and Triton X-100 favored the (alpha 2 beta 2)2 oligomeric form of the receptor. Higher concentrations of Triton X-100 did not **modify** the **polymeric** state of the receptor. In contrast, octylglucoside and Chaps induced an increase in the sedimentation coefficient of the receptor which appeared as (alpha 2 beta 2)3 and (alpha 2 beta 2)4 forms. These alterations in the oligomerization status of the insulin receptor may explain the deleterious effects observed with both Chaps and octylglucoside at higher concentrations.

3/3,AB/35 (Item 35 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

07181564 92119724 PMID: 1769066
Recent progress in protein and peptide delivery by noninvasive routes.
Wearley L L
Schering-Plough Corp., Kenilworth, NJ 07033.
Critical reviews in therapeutic drug carrier systems (UNITED STATES) **1991**, 8 (4) p331-94, ISSN 0743-4863 Journal Code: 8511159
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Much progress has been made in the last 5 years toward delivery of protein and peptide drugs by noninvasive routes. The obstacles of instability, poor absorption, rapid metabolism, and nonlinear pharmacokinetics are great challenges for which some solutions are now emerging. Structural **modifications** of the protein by chemical or recombinant means have improved stability and minimized enzymatic cleavage in some cases. Protection of the protein or peptide drug via **liposomes** or **polymers** also offers a means for increasing stability and prolonging half-life. Novel permeation enhancers, which show minimal irritation to mucosal membranes, have become available and show promise for increasing absorption of proteins delivered by a number of noninvasive routes. There are examples in which several of these methods have been used concomitantly to achieve maximum effect; for instance, a bioadhesive microsphere formulation containing a novel permeation enhancer was used to maximize nasal delivery of insulin. Therefore, general methods exist whereby delivery by any noninvasive route may be improved. In some cases, choice of the best route of delivery for a particular drug makes the difference between success and failure. A comparison of the enzyme activity at the various sites of delivery is helpful and, fortuitously, the enkephalins, model peptides whose rate of cleavage and type of degradation products offer information about the type and activity of enzymes present, have been studied extensively. This work is reviewed for each delivery site as are the effects of coadministration of enzyme inhibitors. Permeation enhancers and examples for their use at each site of delivery are presented. The use of **polymers** for bioadhesion and for protection from metabolism at various sites is reviewed. Since systemic delivery of proteins via the pulmonary route is now receiving more attention, special emphasis is given to that work. Generally, the focus is on work published or presented since 1988, since publications prior to that date have already been thoroughly reviewed. The studies presented indicate that the problems of delivering protein and peptide drugs by noninvasive means can be minimized; although delivery by these routes still may not be bioequivalent to invasive methods, the convenience to the patient will, in some cases, outweigh the demand for complete bioequivalence.

3/3,AB/36 (Item 36 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07093776 92026562 PMID: 1928455
Targeting of macromolecular carriers and **liposomes** by antibodies to myosin heavy chain.
Klibanov A L; Khaw B A; Nossiff N; O'Donnell S M; Huang L; Slinkin M A; Torchilin V P
Institute of Experimental Cardiology, Moscow, USSR.
American journal of physiology (UNITED STATES) Oct **1991**, 261 (4 Suppl) p60-5, ISSN 0002-9513 Journal Code: 0370511
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Macromolecular carriers and **liposomes** were covalently coupled to

monoclonal antibodies against cardiac myosin heavy chain. Deferoxamine-**modified polymers** bound tightly with 67Ga and 68Ga radioisotopes. Ternary deferoxamine-polylysine antibody conjugates specifically targeted the radioisotopes to a myosin-coated microplate. Scatchard analysis revealed a high affinity of the conjugate for the target with a Kas of approximately 10(8) M-1. **Liposomes** that contained immobilized antimyosin antibodies were targeted specifically to the myosin-coated plate. Additional coating of these **liposomes** with polyethylene glycol reduced specific binding to the target in vitro. However, because of the presence of polyethylene glycol on the surface of **liposomes**, these **liposomes** had a long half-life and slowly cleared from the blood-stream after intravenous injection. These immunoliposomes showed up to 16- to 18-fold specific localization to the necrotic areas of the myocardium in rabbits with experimental infarction.

3/3,AB/37 (Item 37 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06782884 91093922 PMID: 2266477
Effect of surfactants on the stability of **modified** egg-yolk phosphatidyl choline **liposomes**.
Alamelu S; Rao K P
Biomaterials Laboratory, Central Leather Research Institute, Madras, India.
Journal of microencapsulation (ENGLAND) Oct-Dec **1990**, 7 (4) p541-51, ISSN 0265-2048 Journal Code: 8500513
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Disintegration by surfactants on egg-yolk phosphatidyl choline (PC) vesicles, stabilized with polycholesteryl methacrylate and carboxy methyl chitosan, was investigated by measuring the amount of marker dye (bromothymol blue) released from the vesicles. In all the studies at pH 7.4 anionic and nonionic surfactants caused vesicle disintegration at low concentrations while cationic surfactants produced breakdown of vesicles at high concentrations. It was found that the **modified liposomes** disintegrated in the following order: **Polymeric liposomes** less than carboxymethyl chitosan coated/stearic acid/oleic acid containing PC **liposomes** less than cholesteryl methacrylate monomer containing PC **liposomes**/PC **liposomes** **Polymeric liposomes** were found to be the most stable compared with all other types. This may be explained due to the filling of the pores in the lipid structure which in turn block the surfactant penetration into phospholipid bilayers. In contrast to unsaturated fatty acid (oleic acid) saturated fatty acid (stearic acid) containing **liposomes** are more stable.

3/3,AB/38 (Item 38 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06706517 91019409 PMID: 2218494
New methods of drug delivery.
Langer R
Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge 02139.
Science (UNITED STATES) Sep 28 **1990**, 249 (4976) p1527-33, ISSN 0036-8075 Journal Code: 0404511
Contract/Grant No.: GM 26698; GM; NIGMS
Document type: Journal Article; Review; Review Literature
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Conventional forms of drug administration generally rely on pills, eye drops, ointments, and intravenous solutions. Recently, a number of novel drug delivery approaches have been developed. These approaches include drug **modification** by chemical means, drug entrapment in small vesicles that are injected into the bloodstream, and drug entrapment within pumps or **polymeric** materials that are placed in desired bodily compartments (for example, the eye or beneath the skin). These techniques have already led to delivery systems that improve human health, and continued research may revolutionize the way many drugs are delivered.

3/3,AB/39 (Item 39 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05745801 88161656 PMID: 3348479
Measurement of **liposome**-released ferrocyanide by a dual-function **polymer modified** electrode.
Kannuck R M; Bellama J M; Durst R A
Analytical chemistry (UNITED STATES) Jan 15 **1988**, 60 (2) p142-7, ISSN 0003-2700 Journal Code: 0370536
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

3/3,AB/40 (Item 40 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05679914 88106318 PMID: 2447870
Influence of phosphatidylserine on endogeneous RNA synthesis in isolated rat liver nuclei.
Capitani S; Caramelli E; Matteucci A; Santi P; Mottola M R; Manzoli F A
Istituto di Anatomia Umana Normale, Universita di Ferrara, Italy.
Basic and applied histochemistry (ITALY) **1987**, 31 (3) p389-412, ISSN 0391-7258 Journal Code: 7910664
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The possible involvement of anionic phospholipids in the transcriptional process was studied in isolated rat liver nuclei synthesizing RNA in the presence of phosphatidylserine, which was employed in the form of multillamellar **liposomes** as a means of delivering the lipid to the nuclei in aqueous medium. The divalent ion requirement for RNA synthesis and the properties of the incubation mixture were not significantly **modified** by the phospholipid, which increased the rate and the extent of the incorporation of 3H-UMP without changing the endogeneous degradation pattern of the product or affecting the activity of a particular RNA **polymerase** , as indicated by the sensitivity to amanitin. The thin layer chromatography analysis of the alkaline hydrolysates of the RNA showed that the stimulation involved an increase of the total polyribonucleotide elongation rate. The size of the product was essentially unchanged in the presence of phosphatidylserine, as demonstrated by the qualitative overlapping of the sedimentation profiles of control and lipid treated samples in formamide-sucrose gradients. The release of the H1 fraction from intact nuclei occurring with phosphatidylserine indicated that the DNA template availability was increased by a partial removal of the restrictions imposed by histones, as suggested also by the comparison with heparin and Sarkosyl. These evidences, together with the data accumulated on the occurrence of lipids in chromatin and nuclear matrix, and on their changes related to cell growth, differentiation and malignant transformation, allow a better definition of the role that phospholipids might play in regulating the DNA template availability in the cell.

3/3,AB/41 (Item 41 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05620937 88046058 PMID: 3673706
Unfolding of nucleosome core induced by phosphatidylserine.
Manzoli F A; Cocco L; Maraldi N M; Capitani S; Barnabei O
Institute of Human Anatomy, Universities of Bologna, Italy.
Advances in enzyme regulation (ENGLAND) **1987**, 26 p271-83,
ISSN 0065-2571 Journal Code: 0044263
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The main experimental findings on the actual presence of lipids among the minor chromatin components are revised and discussed especially in the light of the reported effects that exogenous lipids induce in DNA and RNA synthesis by using purified templates. Moreover, all the available evidence of the influence of phospholipid **liposomes** on the activities and structure of isolated nuclei are reported. In order to further clarify the possible mechanism by which phospholipids could affect gene expression, the **modifications** at the nucleosome core level have been investigated by means of IAF staining and electron microscopy. The results obtained indicate that the increased transcriptional activity induced by PS MLV in isolated nuclei requires both the removal of histone H1, which causes the unfolding of the solenoid into the nucleosome fiber configuration of the chromatin, and the subsequent splitting of the H3 dimer. This latter process, monitored by IAF accessibility to H3 in isolated nucleosomes incubated with PS, causes the transition from the nucleosome to the lexosome structure, which is the configuration favoring the activity of RNA **polymerases**.

3/3,AB/42 (Item 42 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05497301 87246722 PMID: 2885196
Modification of the ultrastructure of Entamoeba histolytica after phagocytosis of **liposomes** loaded with phalloidin.
Trudel P; Gicquaud C
European journal of cell biology (GERMANY, WEST) Apr **1987**, 43 (2) p195-202, ISSN 0171-9335 Journal Code: 7906240
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The specific actin-interacting drug phalloidin has been introduced into the cytoplasm of a highly motile amoeba, Entamoeba histolytica, by a new technique: the phagocytosis of **liposomes** containing phalloidin. After ingestion of these **liposomes**, two important **modifications** of the ultrastructure of the amoeba were observed. First, large nodules of densely packed fine filaments are formed, which may be due to the **polymerization** of actin induced by the release of phalloidin within the cell's cytoplasm. Second, phalloidin induces the proliferation of ribosome crystals known as chromatoid bodies in encysted cells. This formation could be the direct consequence of the action of phalloidin on actin, where filaments form and ribosomes detach from the original oligo or **polymers** . However, it could also result from an unspecific toxic effect on the amoeba which, under physiological stress, starts to encyst and show multiplication of these chromatoid bodies upon encystment.

3/3,AB/43 (Item 43 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

05375569 87123885 PMID: 3468778
Effect of phospholipids on transcription and ribonucleoprotein processing in isolated nuclei.
Capitani S; Cocco L; Maraldi N M; Papa S; Manzoli F A
Advances in enzyme regulation (ENGLAND) **1986**, 25 p425-38, ISSN 0065-2571 Journal Code: 0044263
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The response of isolated rat liver and murine erythroleukemia nuclei to phospholipid **liposomes** has been monitored with different techniques, by studying the endogenous RNA synthesis, the release of transcripts in the medium, the pattern of acid-extractable nuclear proteins and the ultra-structural morphology. Total transcription in rat liver and beta-globin mRNA synthesis in MEL nuclei are increased by PS and reduced by PC. These changes of RNA **polymerase** activity, and the transport of RNAs from nucleus as well as the nuclear protein changes, correlate with structural transitions which occur in both types of nuclei, consisting of euchromatization with loss of RNP particles in the case of PS and opposite effects with PC. The significance of these **modifications** in relationship to the possible involvement of phospholipids in the control of gene expression is discussed.

3/3,AB/44 (Item 44 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05370804 87103039 PMID: 3542244
Synthetic carriers of oxygen.
Dellacherie E; Labrude P; Vigneron C; Riess J G
Critical reviews in therapeutic drug carrier systems (UNITED STATES) **1987**, 3 (1) p41-94, ISSN 0743-4863 Journal Code: 8511159
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
During the last decade, construction of artificial carriers of oxygen for transfusion purposes has evolved in three main directions, which can be reviewed as follows. The first approach consists of **modifying** hemoglobin (Hb), the natural oxygen carrier, in order to lower its oxygen affinity and increase its intravascular persistence. To achieve this aim, two basic procedures have been used: molecular and environmental **modification**. In the first case, Hb is **modified** with chemical reagents; the second requires encapsulation of Hb to obtain artificial erythrocytes. The second approach is based on the use of synthetic oxygen-carrying chelates that mimic the oxygenation function of Hb. The main products in this class are metalloporphyrins, whose chemical environment is designed to render them efficient as reversible carriers of oxygen in vivo. Finally, the third approach deals with the perfluorochemicals used in emulsified form. Perfluorochemical liquids are excellent gas solvents, but some problems remain unsolved with regard to their development as oxygen carriers in vivo: low O2 dissolving capacity, toxicity, and excretion.

3/3,AB/45 (Item 45 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05103514 86161724 PMID: 3913530
Liposomes as targetable drug carriers.
Torchilin V P

Critical reviews in therapeutic drug carrier systems (UNITED STATES) **1985**, 2 (1) p65-115, ISSN 0743-4863 Journal Code: 8511159
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The general problem of targeted drug transport is critically reviewed and three principle components of targeted systems are discussed: the target, the vector molecule, and the carrier. Different systems of drug targeting are briefly described: local drug application, chemical **modification** of the drug molecule, physical targeting under the action of pH, temperature, or magnetic field. The idea of a vector molecule is discussed and different methods of vector molecule coupling with the drug are reviewed (direct coupling, coupling via spacer group or **polymer** molecule, etc.). It is shown that the most promising approach seems to be the use of a drug-containing microcontainer with the vector molecule immobilized on its outer surface. Different types of microcontainers are briefly described: microcapsules, cell hosts, and **liposomes**. The advantages of **liposomes** as drug containers are shown and the main problems of their use for drug targeting in vitro and in vivo conditions are discussed. One of the most important problems is the problem of vector molecule immobilization on **liposome** surfaces. The principle four different immobilization methods: adsorbtion, incorporation, covalent binding, and hydrophobic binding. Targeted **liposome** transport is described in model systems, cell cultures, and experimental animals. It is shown that targeted **liposomes** may release a drug via diffusion, lysis, or endocytosis by appropriate cells. The problems of targeted **liposome** technology and clinical application are analyzed.

3/3,AB/46 (Item 46 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04544935 84234036 PMID: 6733788

Response of isolated nuclei to phospholipid vesicles: analysis of the nuclear proteins after treatment with phosphatidylserine and phosphatidylcholine and comparison with heparin.

Capitani S; Cocco L; Matteucci A; Caramelli E; Papa S; Manzoli F A
Cell biology international reports (ENGLAND) Apr **1984**, 8 (4) p289-96, ISSN 0309-1651 Journal Code: 7708050
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Phospholipid **liposomes** affect the histone pattern of isolated rat liver nuclei. Multilamellar vesicles (MLV) obtained with phosphatidylserine (PS) release a large amount of the lysine rich histones, while those obtained with phosphatidylcholine (PC) do not induce significant changes with respect to controls. This different response has been compared to the effects obtained with Heparin, which slightly **modifies** the relative ratio of the histone fractions. These data might account for the mode by which phospholipids induce transitions of the chromatin structure and changes of the endogenous RNA **polymerase** activity.

3/3,AB/47 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10665915 BIOSIS NO.: 199799287060

Comparative study of the association of intraconazole with colloidal drug carriers.

AUTHOR: De Chasteigner Stephanie; Fessi Hatem; Devissaguet Jean-Philippe(a); Puisieux Francis

AUTHOR ADDRESS: (a)URA CNRS 1218, Faculte de Pharmacie, Universite de Paris XI, 5 avenue Jean-Baptiste Clement, 921**France
JOURNAL: Drug Development Research 38 (2):p125-133 **1996**
ISSN: 0272-4391
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In the present study, the association of a new hydrophobic triazole derivative, itraconazole, with intravenously compatible drug carriers (**liposomes**, cholesterol complexes, nanospheres) was evaluated and the different association yields compared. We tried to elucidate the mechanism of drug-carrier association by means of dilution and zeta potential measurement in the most promising formulations. The different lipid-based drug carriers yielded low association efficiencies (lt 0.6%), whereas itraconazole loading into chemically **modified** beta-cyclodextrin nanospheres reached 6.8% (0.170 mg/mL). The longer the hydrophobic chain linked to the beta-cyclodextrin, the higher the association of itraconazole within the nanospheres. The highest association yields, 4.1% (0.510 mg/mL), were obtained with nanospheres composed of the most hydrophobic **polymer** tested, poly-epsilon-caprolactone, and a negatively charged steroidal surfactant, sodium deoxycholate. Itraconazole seems to be both included in the matrix (40%) and adsorbed at the surface of the nanospheres (60%). This may explain the nanosphere instability with time because of continuous itraconazole desorption from the nanospheres, although the nanosphere mean size remained unchanged. The enhanced association yields observed with sodium deoxycholate were not the result of electrostatic attraction between itraconazole (a weak base) and the negatively charged surfactant but rather to stronger hydrophobic interactions between itraconazole and sodium deoxycholate, and to increased specific area of sodium deoxycholate-coated nanospheres. This latter was due to the smaller mean diameter (80 nm) of the sodium deoxycholate-coated nanospheres compared with non ionic surfactant-coated nanospheres (130 nm).

1996

3/3,AB/48 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10615100 BIOSIS NO.: 199699236245
New preparations of insulin highly resistant to proteolysis (review).
AUTHOR: Valuev L I; Valuev I L; Sytov G A
AUTHOR ADDRESS: A.V. Topchiev Inst. Petrochem. Synth., Russ. Acad. Sci., Leninskii pr. 29, Moscow 117912**Russia
JOURNAL: Prikladnaya Biokhimiya i Mikrobiologiya 32 (4):p371-381
1996
ISSN: 0555-1099
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: Russian; Non-English
SUMMARY LANGUAGE: Russian; English

ABSTRACT: Chemical methods that accelerate the transport of insulin and other polypeptides across biological membranes and increase their resistance to enzymatic hydrolysis are reviewed. These methods include chemical **modification** of insulin macromolecules, the use of compounds that increase the permeability of biological membranes or inhibit enzymatic proteolysis, the hormone immobilization in a **polymer** coat protecting it against the aggressive environment, the incorporation of insulin into **liposomes**, etc. The advantages and drawbacks of these methods are analyzed, and promising lines of research in this field of applied biochemistry are described.

1996

3/3,AB/49 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10583549 BIOSIS NO.: 199699204694
Application of membrane and film to medical and pharmaceutical fields.
AUTHOR: Miyajima Koichiro
AUTHOR ADDRESS: Fac. Pharm. Sci., Kyoto Univ., 46-29
Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto-shi 606**Japan
JOURNAL: Membrane 20 (4):p246-254 **1995**
ISSN: 0385-1036
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: Japanese; Non-English
SUMMARY LANGUAGE: English

ABSTRACT: **Modified** natural and synthetic **polymers** and phospholipids have been studied as membrane materials in medical and pharmaceutical fields. Chitin prepared from the carapace of carb and shrimp is biodegradable **polymer** of acetylglucosamine and easily forms a film and fiber from solution. The chitin film protects from an attack of bacteria, when covered on the wounded site and accelerates the recovery. **Polymer** membranes have been used as materials of microcapsules containing drugs inside, through oral, subcutaneous and intramuscular administrations. These microcapsules administered orally are capable to release drugs at targeting organ in time-dependent manner. Biodegradable **polymer** microcapsule implanted in muscle through injection, releases drugs for over 4 weeks at a constant rate. Biodegradable and biocompatible phospholipids has been applied for the preparations of intravenous administrations as a **liposome** and a microsphere. **Liposomes** and microspheres accumulate generally in reticuloendothelial system (RES). Recently RES-avoiding **liposome** has been developed by the **modification** of liposomal surface with polyethylene glycol and applied for an artificial red blood cell with undated hemoglobin. Lipid microsphere containing prostaglandin E-1 and anti-inflammation drug had been applied for the cure of inflammation diseases, because the inflammation sites are macrophage-rich.

1995

3/3,AB/50 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10423228 BIOSIS NO.: 199699044373
Surface **modification** of continuously extruded contrast-carrying **liposomes**: Effect on their physical properties.
AUTHOR: Schneider T; Sachse A(a); Leike J; Roessling G; Schmidtgen M; Drechsler M; Brandl M
AUTHOR ADDRESS: (a)PHZE Parenterale Arzneiformen, Schering AG, 13342 Berlin **Germany
JOURNAL: International Journal of Pharmaceutics (Amsterdam) 132 (1-2):p 9-21 **1996**
ISSN: 0378-5173
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Surface-**modified**, contrast-carrying **liposomes** were

generated by incorporation of amphipathic **polymers** into the membranes of continuously extruded vesicles. Besides the well described distearoylphosphatidylethanolamine monomethoxypolyethyleneglycol (DSPE-PEG), a new substance, cholesterylhemisuccinate monomethoxypolyethyleneglycol (CholHS-PEG) was tested for the first time. Using the water-soluble radiographic contrast agent iopromide as well as the nuclear magnetic contrast agent Gd-DTPA, the impact of surface **modification** (SM) on **liposome** properties like vesicle size distribution, encapsulation efficiency, zeta potential and storage as well as plasma stability was investigated. In the course of the studies, the molar amount of amphipathic **polymer** employed as well as the time point of SM during the production process were varied. Incorporation of both, DSPE-PEG and CholHS-PEG into the lipid films formed before continuous extrusion resulted in a concentration-dependent decline of encapsulation efficiencies. When SM was carried out after vesicle formation, the observed effect diminished and even disappeared, as soon as PEG-coating was carried out after the last extrusion step. However, when using the latter procedure with DSPE-PEG, mean vesicle diameters showed a strong increase in the course of the pegylation process. The extent of bilayer **modification** was studied by zeta potential measurements of **liposomes** containing the negatively charged phospholipid SPG. In the presence of PEG-derivatives the high zeta potentials of unmodified vesicles were significantly reduced, irrespective of whether SM was carried out before, during or after extrusion. This result indicated a successful association of the PEG-derivatives with liposomal bilayers for all procedures. For CholHS-PEG complete incorporation into **liposomes** after extrusion could be demonstrated using gel filtration. Stability testing revealed an unchanged macroscopic appearance, encapsulation efficiency and vesicle size distribution of unmodified and CholHS-bearing **liposomes** after 4 months' storage at 2-8 degree C. In contrast to this, DSPE-PEG-containing vesicles displayed a pronounced size increase when SM was carried out during extrusion. Another important effect of DSPE-PEG incorporation was found during plasma stability experiments. Whereas CholHS-PEG-carrying and unmodified **liposomes** had similar leakage rates in human plasma, DSPE-PEG caused a concentration-dependent decrease in plasma stability, but only when SM had been carried out before extrusion. Altogether, from a merely technological point of view, CholHS-PEG revealed superior properties over DSPE-PEG for SM of continuously extruded contrast-carrying **liposomes**.

1996

3/3,AB/51 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10172704 BIOSIS NO.: 199698627622
In vivo visualizing of organs and tissues with **liposomes**.
AUTHOR: Torchilin Vladimir P(a); Trubetskoy Vladimir S
AUTHOR ADDRESS: (a)Cent. Imaging Pharmaceutical Res., Dep. Radiology, Mass. General Hosp., Harvard Med. Sch., 149 1**USA
JOURNAL: Journal of Liposome Research 5 (4):p795-812 **1995**
ISSN: 0898-2104
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The application of **liposomes** as carriers for imaging agents is considered. **Liposomes** loaded with the appropriate contrast agents have been shown to be suitable for gamma-, magnetic resonance (MR), computed tomography (CT) and ultrasound imaging. The methods are briefly described to prepare **liposomes** loaded with different

contrast agents, as well as some data on their biodistribution. The application of contrast-loaded **liposomes** for liver/spleen, tumor, lymph nodes, infection and inflammation sites, myocardial infarction, and blood pool imaging is briefly reviewed together with some data available on the use of **liposome** for the ophthalmological imaging. New trends in the use of contrast-loaded **liposomes** are also considered, such as the application of long-circulating **polymer-modified liposomes** for imaging purposes and development of new lipid-coated **liposome**-like contrast agents.

1995

3/3,AB/52 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09926686 BIOSIS NO.: 199598381604
Biophysical view of the role of interfaces in biomolecular recognition.
AUTHOR: Cevc Gregor
AUTHOR ADDRESS: Med. Biophysik, Technishe Univ. Muenchen, Klinikum r.d.I., Ismaningerstr. 22, D-81675 Muenchen, E.U.**Germany
JOURNAL: Biophysical Chemistry 55 (1-2):p43-53 **1995**
ISSN: 0301-4622
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Molecular recognition plays a key role in life. Macromolecular interactions at and with interfaces are of paramount importance in this respect. It is therefore crucial to understand and quantify the forces near the surfaces of biological interest in sufficient detail. Specific binding of large molecules, such as antibodies, is affected by the proximity of polar surfaces, for example. On the one hand, the presence of the net surface charges may raise or lower the local macromolecular concentration depending on the relative sign of the charges involved. On the other hand, the ligands attached to strongly polar surfaces always attract and bind their corresponding antibodies less efficiently than the corresponding dissolved molecules. The reason for this is the non-Coulombic repulsion between the ligand-presenting polar surface and the approaching macromolecule. This force is promoted by the surface hydrophilicity and the width of the interfacial region. A simple, direct hydration force is seldom, if ever, seen in such systems. (This is owing to the very short range (A-h = 0.1 nm) of pure hydration force.) The non-specific adsorption of proteins to the lipid bilayer is also little affected by the overall repulsion between the macromolecule and the bilayer surface; such an adsorption is governed more by the number of defects and/or by the availability of the hydrophobic binding sites in the interfacial region. Artificial lipid membranes typically offer numerous such binding sites to the surrounding macromolecules. Multiple non-specific protein adsorption, which results in partial macromolecular denaturation or complement activation, is therefore one of the main reasons for the rapid elimination of lipid vesicles from the blood stream in vivo. To promote the circulation time of an intravenously injected lipid suspension it is therefore necessary to **modify** the surfaces of their constituent lipid bilayers. Increasing the surface net charge density and/or increasing the bilayer surface hydrophilicity is of little use in this respect. In order to affect the non-specific bilayer-protein interactions significantly, an optimal number of water-soluble, short and sufficiently mobile **polymers** must be attached to the lipid head-groups. These **polymers** then increase the repulsive barrier of the membrane surface dramatically, due to the generation of a thick and mobile as well as strongly hydrated interface. Owing to this, the affinity for proteins of the resulting surface is lowered and the

surface-induced protein denaturation or complement insertion is hampered. **Polymer**-coated **liposomes**, consequently, are not attractive for the phagocytic cells. Such **liposomes**, consequently, remain in the blood circulation much longer than simple lipid vesicles; the former, consequently, may spontaneously accumulate in tumors.

1995

3/3,AB/53 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09712195 BIOSIS NO.: 199598167113
Haemoglobin-based red blood cell substitutes.
AUTHOR: Waschke K F
AUTHOR ADDRESS: Inst. Anaesthesiol. Oper. Intensivmed., Fak. Klin. Med. Mannheim Univ. Heidelberg, Klin. Mannheim, T**Germany
JOURNAL: Anaesthesist 44 (1):p1-12 **1995**
ISSN: 0003-2417
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: German; Non-English
SUMMARY LANGUAGE: German; English

ABSTRACT: Although the attempts to develop an oxygen-carrying alternative to red blood cells (RBC) have spanned the last 100 years, it has proven difficult to develop a clinically useful haemoglobin-based oxygen carrier. Four major problems have been shown to compromise the use of haemoglobin outside the RBC as an oxygen carrier: (1) the increased oxygen affinity due to the loss of 2,3-diphosphoglycerate (2) dissociation into dimers and monomers with consequent renal and capillary loss of hemoglobin; (3) insufficient concentrations of prepared solutions under iso-oncotic conditions, and thereby reduced oxygen-carrying capacity; and (4) toxicity. Most of these limitations have been overcome by different **modifications** of haemoglobin, including pyridoxylation, intra- and intermolecular cross-linking, **polymerisation**, **liposome** encapsulation, conjugation to inert macromolecules, and genetic engineering. Questions of toxicity are not completely answered at present, especially with regard to renal toxicity, interactions with the nitric oxide system, and antigenicity. Therefore, the issues preventing clinical application are those of safety and not of efficacy of haemoglobin-based RBC substitutes. Potential clinical applications include fluid resuscitation, treatment of anaemia and ischaemia, support in extracorporeal circulation, and organ preservation. Based on promising and reproducible results obtained from animal studies, clinical phase I and II trials with newer haemoglobin solutions have been started in the United States. Substantial knowledge has been gained in the development, production, and evaluation of haemoglobin-based oxygen carriers during the past years. It will probably not take another century before oxygen-carrying RBC substitutes will become available for clinical use.

1995

3/3,AB/54 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09591305 BIOSIS NO.: 199598046223
New Amphipathic **Polymer**-Lipid Conjugates Forming Long-Circulating Reticuloendothelial System-Evading **Liposomes**.
AUTHOR: Woodle Martin C; Engbers Charles M; Zalipsky Samuel(a)

AUTHOR ADDRESS: (a)Liposome Tech. Inc., 960 Hamilton Court, Menlo Park, CA 94025**USA
JOURNAL: Bioconjugate Chemistry 5 (6):p493-496 **1994**
ISSN: 1043-1802
DOCUMENT TYPE: Letter
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Lipid-conjugates of two amphipatic **polymers**, poly(2-methyl-2-oxazoline) (PMOZ) and poly(2-ethyl-2-oxazoline) (PEOZ) (degree of **polymerization** apprxeq 50) were synthesized by linking glutarate esters of the **polymers** to distearoylphosphatidylethanolamine (DSPE) or alternatively by termination of the **polymerization** process with DSPE. Surface-**modified** **liposomes** (90 +- 5 nm) prepared from either conjugate (5 mol % of total lipid) were injected into rats and followed by blood level and tissue distribution measurements. Both **polymers** PEOZ and PMOZ were found to convey long circulation and low hepatosplenic uptake to **liposomes** to the same extent as polyethylene glycol (PEG), the best known material for this purpose. This is the first demonstration of protection from rapid recognition and clearance conveyed by alternative **polymers**, which s equal to the effect of PEG.

1994

3/3,AB/55 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09447113 BIOSIS NO.: 199497455483
New approaches in the chemical design of Gd-containing **liposomes** for use in magnetic resonance imaging of lymph nodes.
AUTHOR: Trubetskoy Vladimir S; Torchilin Vladimir P
AUTHOR ADDRESS: Cent. Imaging Pharm. Res., Mass. Gen. Hosp.-East, 149 13th St., Charlestown, MA 02129**USA
JOURNAL: Journal of Liposome Research 4 (2):p961-980 **1994**
ISSN: 0898-2104
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Several approaches to improve Gd-containing **liposomes** as magnetic resonance contrast medium for the visualization of lymph nodes are discussed. The **modification** of the **liposome** surface with a **polymer** was chosen as a chemical solution to control the contrast enhancement properties of the medium. It was found that **liposome** **modification** with Gd-diethylenetriaminepentaacetic acid (DTPA)-polylysine-based chelating **polymer** can increase several fold the metal load per vesicle, while surface **modification** with polyethylene glycol (PEG) might lead to the increased relaxivity of paramagnetic vesicles. Examples are given on how chemical **modification** of the **liposome** surface can improve the performance of Gd-containing **liposomes** in the visualization of lymph nodes.

1994

3/3,AB/56 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09300060 BIOSIS NO.: 199497308430

Photosensitive **liposomes**.
AUTHOR: Bennett Doyle E; Lamparski Henry; O'Brien David F(a)
AUTHOR ADDRESS: (a)Carl S. Marvel Lab., Dep. Chemistry, Univ. Ariz., Tucson, AZ 85721**USA
JOURNAL: Journal of Liposome Research 4 (1):p331-348 **1994**
ISSN: 0898-2104
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Photosensitive lipids and **liposomes** may be designed by a variety of strategies. These include the photochemical **modification** of individual lipids in the bilayer; the photoinduced change in the association of polyelectrolytes with **liposomes**; and the photoinitiated **polymerization** of some or all of the lipids in the **liposome**. The interaction of light with photosensitive **liposomes** can cause bilayer reorganization with possible applications in imaging, sensing, as well as therapeutics. The latter is the focus of this review.
1994

3/3,AB/57 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09170157 BIOSIS NO.: 199497178527
Calorimetric studies on tolmetin release from poly-DL-lactide microspheres to lipid model membrane.
AUTHOR: Castelli Francesco(a); Conti Bice; Puglisi Giovanni; Conte Ubaldo; Mazzone Gioacchino
AUTHOR ADDRESS: (a)Dip. Sci. Chim., Viale A. Doria 6, 95125 Catania**Italy
JOURNAL: International Journal of Pharmaceutics (Amsterdam) 103 (3):p 217-223 **1994**
ISSN: 0378-5173
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The aim of this work was to study the rate of release of an NSAI agent from poly-DL-lactide (PDLLA) microspheres, by evaluating the effect of the drug on the thermotropic behaviour of dimyristoylphosphatidylcholine **liposomes** (DMPC), selected as a model membrane. Polylactide microspheres loaded with 1-methyl-5-p-toluoylpyrrole-2-acetic acid (tolmetin) were prepared by the spray-drying method. Samples made of **liposomes** charged with free drug and suspensions of blank **liposomes** added to weighed amounts of tolmetin-loaded microspheres were analyzed by DSC. Calorimetric analyses were performed on samples previously incubated at temperatures below and above the **polymer** glass transition temperature (Tg). Free drug was found to interact with the phospholipidic bilayer by **modifying** its thermotropic behavior. The amount of drug released from the microparticulate to void **liposomes** was quantified by comparing the T-m shift caused by drug release from the **polymeric** system with that due to free drug. The results demonstrate the extent to which the release process is affected by temperature throughout the **polymeric** structure. In conclusion, the calorimetric technique detects changes occurring directly on the adsorption sites and can thus be applied to study slow kinetics directly at the site of drug uptake.

1994

3/3,AB/58 (Item 12 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

09076468 BIOSIS NO.: 199497084838
Use of **polymerized** mixed **liposomes** to study interactions of phospholipase A-2 with membranes.
AUTHOR: Wu Shih-Kwang; Cho Wonhwa(a)
AUTHOR ADDRESS: (a)Dep. Chem., Univ. Ill. Chicago, Chicago, IL 60607-7061** USA
JOURNAL: Biochemistry 32 (50):p13902-13908 **1993**
ISSN: 0006-2960
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: **Polymerized liposomes** of thiol-based phospholipids, 1,2-bis(12-(lipoyloxy)dodecanoyl)-sn-glycero-3-phosphocholine (BLPC) and -phosphoglycerol (BLPG) were used to study interactions of several phospholipases A-2 (PLA-2) with membranes. Large **liposomes** (an average diameter of 100 +- 10 nm) prepared from BLPC or BLPG were readily hydrolyzed by PLA-2. Once **polymerized**, however, these **liposomes** were resistant to the PLA-2 hydrolysis. When **liposomes** were prepared from a mixture of 1-hexadecanoyl-2-(1-pyrenyldecanoyl)-sn-glycero-3-phosphocholine (pyrene-PC) (5 mol%) and BLPC, fluorescence measurements of resulting **polymerized** mixed **liposomes** showed that the pyrene-PC molecules exist solely as monomers without forming a patch and were selectively hydrolyzed by PLA-2. Progress of the hydrolysis can be readily monitored by measuring the change in fluorescence emission at 380 nm in the presence of bovine serum albumin. Rapid and selective hydrolysis of inserted phospholipids in **polymerized** mixed **liposomes** supports the notion that facile migration of a phospholipid substrate from membrane to the active site of enzyme is a critical step in the catalysis of PLA-2. On the basis of these findings, various combinations of **polymerized** mixed **liposomes** were prepared and their hydrolysis by PLA-2 measured. When compared to the substrate specificity of PLA-2s determined using Triton X-100/phospholipid mixed micelles, results from **polymerized** mixed **liposomes** indicate that electrostatic interactions between the interfacial binding site of PLA-2 and membrane surfaces play an important role in the determination of substrate specificity of PLA-2 and in the regulation of PLA-2 activities. Lastly, **polymerized** mixed **liposomes** can serve as a versatile and sensitive PLA-2 assay system in which one can readily **modify** the structure of **polymerized** matrix to create **liposome** surfaces ideal for a specific PLA-2.
1993

3/3,AB/59 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08980727 BIOSIS NO.: 199396132228
The study of the properties of **modified polymerized liposomes** with the new type of glycosyldiglycerides.
AUTHOR: Lyubeshkin A V; Sebyakin Yu L; Evstigneeva R P
AUTHOR ADDRESS: M.V. Lomonosov Inst. Fine Chem. Technol., Moscow**Russia

JOURNAL: Biologicheskie Membrany (Moscow) 10 (4):p431-437 **1993**
ISSN: 0233-4755
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: Russian; Non-English
SUMMARY LANGUAGE: Russian; English

ABSTRACT: The behavior of a new type of glycosyldiglycerides containing sulfhydrilic groups at the aglycon terminal position in phosphocholine **liposomes** with the analogous fatty acid residues is studied. Additional data on the structural organization of phospholipid vesicles upon oxidative **polymerization** under different conditions were obtained, using 31P-NMR spectroscopy. The stability of phosphocholine **polymerized liposomes** and "glycosylated" ones in the presence of Triton X-100 is investigated. the comparative studies of the interaction of the **polymerized liposomes**, containing different carbohydrate determinants (D-glucose, D-galactose, and lactose), with lectin RCA-1 are carried out. It is shown that a more effective binding with lectin occurs in the presence of lactose residues on the vesicle surface.

1993

3/3,AB/60 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08373750 BIOSIS NO.: 000094104254
MODIFIED POLYANIONIC **POLYMERS** FOR ENHANCED CELL MEMBRANE INTERACTION
AUTHOR: SUDA Y; KUSUMOTO S; OKU N; YAMAMOTO H; SUMI M; ITO F; OTTENBRITE R M
AUTHOR ADDRESS: DEP. CHEM., FAC. SCI., OSAKA UNIV., TOYONAKA, OSAKA 560, JPN.
JOURNAL: J BIOACT COMPAT POLYM 7 (3). 1992. 275-287. **1992**
CODEN: JBCPE
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The affinty of poly(maleic acid-alt-2-cyclohexyl-1, 3-dioxepin-5-ene) [poly(MA-CDA)] for cell membranes was improved by grafting hydrophobic groups onto the **polymers**. The members affinity of these **modified** polyanionic **polymers** was characterized by their interaction with negatively charged **liposomes**. The biological activity of the **modified polymers** in vitro was determined with cultured cell lines. The superoxide release from DMSO differentiated HL-60 cells, stimulated by the **modified** poly (MA-CDA), was remarakable compared to the unmodified poly(MA-CDA). This higher activity may be due to the improved affinity of the **modified polymers** for the cell membranes. The long-term cytotoxicity of the **polymers** was examined using J774 cells. It was observed that the **polymers** was cytotoxic at relatively high concentrations, and the cytotoxicity correlated with the improved membrane affinity. In both in vitro tests, the molecular weight of the **modified** poly)MA-CDA) affected the biological response. The higher activites were found for the lower molecular weight **polymers**.

1992

3/3,AB/61 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08131876 BIOSIS NO.: 000093119024
MODIFIED POLYANIONIC **POLYMERS** I. GRAFTING OF HYDROPHOBIC GROUP ONTO POLYMALEIC ACID-ALT-3 4-DIHYDROXYPHENYLPROP-1-ENE TO IMPROVE THE AFFINITY FOR CELL MEMBRANES
AUTHOR: SUDA Y; YAMAMOTO H; SUMI M; OKU N; ITO F; YAMASHITA S; NADAI T;

OTTENBRITE R M
AUTHOR ADDRESS: DEP. CHEM., FAC. SCI., OSAKA UNIV., TOYONAKA, OSAKA 560, JAPAN.
JOURNAL: J BIOACT COMPAT POLYM 7 (1). 1992. 15-24. **1992**
CODEN: JBCPE
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: To improve the affinity of polyanionic **polymers** for cell membranes, several hydrophobic groups were grafted onto poly(maleic acid-alt-3,4-dihydroxyphenylprop-1-ene) [poly(MA-alt-DP)] which has cytotoxic activity. The effect of the degree of substitution of the grafted group to the maleic anhydride residue was also evaluated. Grafted **polymers** were characterized by their partition coefficients, their affinity to **liposomes** and their ability to interact with rat small intestinal epithelial cells. It was found that the cell affinity of the **modified** polyanionic **polymers** could be augmented and controlled by simple grafting.

1992

3/3,AB/62 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07638461 BIOSIS NO.: 000092008405
MACROMOLECULAR PRODRUGS INTERACTION WITH MIXED LIPID MEMBRANE A CALORIMETRIC STUDY OF NAPROXEN LINKED TO POLYASPARTAMIDE INTERACTING WITH PHOSPHATIDYLCHOLINE AND PHOSPHATIDYLCHOLINE-PHOSPHATIDIC ACID VESICLES
AUTHOR: CASTELLI F; GIAMMONA G; RAUDINO A; PUGLISI G
AUTHOR ADDRESS: DEP. SCI. CHIMICHE, UNIV. CATANIA, VIALE ANDREA DORIA 6, 95125 CATANIA, ITALY.
JOURNAL: INT J PHARM (AMST) 70 (1-2). 1991. 43-52. **1991**
FULL JOURNAL NAME: International Journal of Pharmaceutics (Amsterdam)
CODEN: IJPHD
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The thermal behavior of pure dipalmitoylphosphatidylcholine (DPPC) **liposome** or mixed **liposomes** of DPPC with charged dipalmitoylphosphatidic acid (DPPA) and interacting with **polymeric** prodrugs has been investigated by differential scanning calorimetry (DSC). The apolar drug was naproxen (NAP) covalently linked to a water-soluble **polymer** (.alpha.,.beta.-poly(N-hydroxyethyl)-DL-aspartamide (PHEA)). Addition of increasing amounts of NAP to DPPC **liposomes** causes a decrease in the transition temperature (Tm) associated to the gel-to-liquid crystal phase transition with a small decrease in the enthalpy values (.DELTA.H), whereas a corresponding amount of drug contained in the PHEA-adduct **modifies** the **liposome** phase transition by decreasing the .DELTA.H and broadening the peak without Tm variations. These effects have been interpreted as a different interaction of free a **polymer** -bound drug with the lipid bilayer. The drug effect on mixed **liposomes** was also investigated, and evidence of improved interaction of the drug-PHEA adduct with two-component bilayers, which better mimic biological membranes, was found. In order to understand the prodrug-lipid interactions, we modulated the surface charge density of the mixed **liposomes** with Ca2+, while binds strongly to the negatively charged lipid head groups. We observed lateral phase separation, induced by NAP-PHEA adduct and modulated by Ca2+, and the phenomenon was explained in terms of different drug solubility in DPPC-poor and DPPC-rich microdomains. The results are indicative of different interactions of naproxen, either free or bound to a

polymeric carrier, with phospholipid membranes and the ability of Ca2+ to influence the adsorption of the drug.

1991

3/3,AB/63 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07586055 BIOSIS NO.: 000091114844
REGULATION OF MONOLAYER FUSION IN COLORED LIPID MEMBRANES BY POLY-4-VINYLPYRIDINE DERIVATIVES
AUTHOR: RITTER V G
AUTHOR ADDRESS: INST. PROBL. TRANSMS. INF., ACAD. SCI. USSR, MOSCOW, USSR.
JOURNAL: BIOL MEMBR 7 (10). 1990. 1056-1064. **1990**
FULL JOURNAL NAME: Biologicheskie Membrany
CODEN: BIMEE
RECORD TYPE: Abstract
LANGUAGE: RUSSIAN

ABSTRACT: The regulation of coalescence of coloured (thick) phospholipid membranes by poly-N-ethyl-4-vinylpyridinium bromide (PVP) has been studied as a function of PVP **polymerization** degree, charge density and concentration. The membranes were formed from the decane solution of azolectin. The rate of monolayer fusion was measured basing on the membrane coalescence time Tc, i. e. time span between bringing the membranes into contact and their coalescence detected visually as an instant change in the zone of their contact. Fusion was **modified** by adding PVP into an aqueous solution. It was shown that at pH 7,5 the addition of PVP decreased Tc. At neutral pH, an increase in the PVP concentration led to a shorter Tc. Before PVP concentration attains threshold value, Tc is increasing and then is rapidly diminishing. The inhibitory effect is getting weaker with the increase in the PVP chain length. At the pH 3,2 Tc is no longer dependent on the PVP concentration, while at pH 5,5 the dependence is the same as at neutral pH. The measurement of the electrophoretic mobility of azolectin **liposomes** at pH 5,5 and 3,2 revealed that, firstly, lipid surface was recharged at PVP concentrations distinct from the fusogenic ones, and, secondly, **polymer** adsorption was only weakly pH-dependent. Surface pressure of the lipid monolayer at the air/water interface and the average area of a lipid molecule were growing upon PVP adsorbtion, while the monolayer compressibility decreased. A comparison of the fusogenic potency of PVP differing in charge group density k (100, 65 and 18%) demonstrated the highest efficiency of **polymers** with k-65%. A model is discussed that ascribes fusogenic activity to clasterization of PVP molecules on the lipid monolayer surface.

1990

3/3,AB/64 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07161640 BIOSIS NO.: 000089028283
DELIVERY OF ANTICANCER DRUGS
AUTHOR: ZEE-CHENG R K-Y; CHENG C C
AUTHOR ADDRESS: DEP. PHARMACOL. TOXICOL. THERAP., UNIV. KANSAS CANCER CENT., KANSAS CITY, KANSAS 66103, USA.
JOURNAL: METHODS FIND EXP CLIN PHARMACOL 11 (7-8). 1989. 439-529.
1989
FULL JOURNAL NAME: Methods and Findings in Experimental and Clinical Pharmacology

CODEN: MFEPD
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Chemotherapy is a major therapeutic approach for the treatment of both localized and metastasized cancers. Since anticancer drugs are neither specific nor targeted to the cancer cells, improved delivery of anticancer drugs to tumor tissues in humans appears to be a reasonable and achievable challenge. Scientists are working to increase the availability of drug for tumor uptake by 1) delaying the release preparations for long- lasting actions; 2) using **liposome**-entrapped drugs for prolonged effect or reduced toxicity; 3) administrating inert, non-toxic prodrugs for specific activations at the tumor site; 4) delivering the antibody-mediated drugs; 5) conjugating site-specific carriers to direct the drug to the tumor target. The latter depends heavily on pharmacokinetic investigations. Some success has been achieved in enhancing the efficacy and reducing the toxicity of drugs. Pharmacokinetic and pharmacodynamic considerations are two areas which have been focused toward the quantitative pharmacological studies of anticancer drugs in this manuscript. This review covers biodistribution and elimination, furnishing information on body clearance and unveiling sites of major metabolism; administration of anticancer drugs via various routes for optimal utilization: intra-arterial infusion for localized tumors, intrahecal, intraperitoneal and intrapleural injection for regional cavity administration. Conventional delivery routes, doses, pharmacokinetics data and elimination routes of therapeutic anticancer drugs are tabled. General approaches for delivery of anticancer drugs in achieving therapeutic improvements are outlined and correlated. Mechanism of drug resistance, and specific changes affecting the delivery of available chemotherapeutic agents, as well as the drugs to restore the sensitivities to agents of resistant tumor cells, are discussed. This monograph covers the developments and progress in the delivery of anticancer drugs in two approaches: the theoretical approach, including pharmacokinetic and pharmacodynamic considerations, therapeutic implications and mechanism of drug resistance, and the practical approach, including the physical, chemical, biochemical and physiological considerations. Among these, physical approach for the delivery of anticancer agents to target sites (via microparticulate drug carriers: nanoparticles, **liposomes**, microspheres and activated carbon as well as the magnetic microcapsules) has shown recognizable improvements in prolonging anticancer effects and reducing toxicities. Implantable pumps and reservoirs for regional chemotherapy provide external control of delivery rate. The implanted systems, in general, yield better results than the traditional treatments in the treatment of liver and brain cancer. Chemical approaches for the improvements of drug delivery use prodrugs, biodegradable **polymers** and macromolecular matrix techniques. **Modification** of drug structure aims for better delivery through the action of prodrugs to improve their stability, solubility, tissue penetration properties and drug distribution, and to overcome resistance and alter the pharmacokinetic nature and selective activation at the target cells. The prodrug approach has definitely produced outstanding results in preserving stability, prolonging activity, reducing toxicity of parent drugs, and hopefully, producing active forms at targeted sites. Biodegradable **polymers** have demonstrated their increasing importance in practical applications. The macromolecular matrices approach and the biochemical approach for antibody-mediated drug delivery, although of theoretical interests, are still in the investigational stage. More practical and elegant preparations of components and conjugation to the drug system should be sought so that sufficient amounts of the delivery systems could be accumulated for the evaluation and comparison in humans. Promising results would then change the strategic mirage to a stratagemic miracle to achieve an ideal delivery system of anticancer drugs. A thorough understanding of the physiological features and knowledge would provide leads for improvements

in drug delivery. For instance, transient reversible **modification** of the blood-brain barrier by osmotic opening, verapamil reversal of vincristine resistance, overcoming P388 resistance to adriamycin by nitroxazapine, and the enhancement of chemotherapeutic effects of certain anticancer drugs by an enantomer are some examples of further drug delivery explorations. It is anticipated that future developments will be achieved in these areas through multidisciplinary efforts.

1989

3/3,AB/65 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07037278 BIOSIS NO.: 000089118832
INTERACTION OF MACROMOLECULAR PRO-DRUGS WITH LIPID MODEL MEMBRANE CALORIMETRIC STUDY OF 4 BIPHENYLACETIC ACID LINKED TO ALPHA BETA POLY-N HYDROXYETHYL-DL-ASPARTAMIDE INTERACTING WITH PHOSPHATIDYLCHOLINE VESICLES
AUTHOR: CASTELLI F; GIAMMONA G; PUGLISI G; CARLISI B; GURRIERI S
AUTHOR ADDRESS: DIPARTIMENTO DI SCIENZE CHIMICHE, UNIVERSITA DI CATANIA, VIALE ANDREA DORIA 6, 95125 CATANIA, ITALY.
JOURNAL: INT J PHARM (AMST) 59 (1). 1990. 19-26. **1990**
FULL JOURNAL NAME: International Journal of Pharmaceutics (Amsterdam)
CODEN: IJPHD
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The effect of 4-biphenylacetic acid (BPAA) covalently linked to .alpha.,.beta.-poly(N-hydroxyethyl)-DL-aspartamide (PHEA) on the thermotropic properties of dipalmitoylphosphatidylcholine (DPPC) **liposomes** was investigated by differential scanning calorimetry (DSC). Addition of increasing amounts of PHEA-BPAA adduct to a suspension of phospholipid vesicles **modified** the thermotropic gel-to-liquid crystalline phase transition by decreasing the enthalpy changes .DELTA.H with concomitant broadening of the peak without variations in the transition temperature (Tm). These effects are interpreted in terms of a deep interaction of BPAA bound to the **polymer** with the apolar moiety of the lipid bilayer. The amount of drug able to suppress the phase transition was estimated by plotting the enthalpy changes of the transition vs mole ratio of added drug, and extrapolating to .DELTA.H = 0. The trend in the .DELTA.H values yields a possible 1:1 stoichiometry for the interaction between drug and phospholipid. Experiments carried out at different pH values provided information about the species involved in the interaction with DPPC **liposomes**. Similar results can be expected in the case of the cell membrane.

1990

3/3,AB/66 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

05961123 BIOSIS NO.: 000035052486
DUAL-FUNCTION **POLYMER-MODIFIED** ELECTRODE FOR THE MEASUREMENT OF **LIPOSOME**-RELEASED FERROCYANIDE
AUTHOR: DURST R A; KANNUCK R M
AUTHOR ADDRESS: CENT ANALYTICAL CHEM., NATL. BUREAU OF STANDARDS, GAITHERSBURG, MD. 20899.
JOURNAL: THIRD CHEMICAL CONGRESS OF NORTH AMERICA HELD AT THE 195TH AMERICAN CHEMICAL SOCIETY MEETING, TORONTO, ONTARIO, CANADA, JUNE 5-10, 1988. ABSTR PAP CHEM CONGR NORTH AM 3 (1). 1988. ANYL 85. **1988**
CODEN: ABPAE

DOCUMENT TYPE: Meeting
RECORD TYPE: Citation
LANGUAGE: ENGLISH
1988

3/3,AB/67 (Item 21 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

04931122 BIOSIS NO.: 000031006254
MODIFYING THE RESPONSE OF EHRLICH ASCITES TUMOR CELLS TO NITROGEN MUSTARD BY VINCRISTINE CALCIUM AND **LIPOSOMES**
AUTHOR: RITTER C; RUTMAN R J
AUTHOR ADDRESS: SCH. VET. MED. UNIV. PA. 19104.
JOURNAL: 70TH ANNUAL MEETING OF THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY, ST. LOUIS, MO., USA, APR. 13-18, 1986. FED PROC 45 (3). 1986. 466. **1986**
CODEN: FEPRA
DOCUMENT TYPE: Meeting
RECORD TYPE: Citation
LANGUAGE: ENGLISH
1986

3/3,AB/68 (Item 22 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

02368287 BIOSIS NO.: 000065025317
INTERACTION OF **LIPOSOMES** WITH POLYMORPHONUCLEAR LEUKOCYTES PART 2 STUDIES ON THE CONSEQUENCES OF INTERACTION
AUTHOR: DAHLGREN C; KIHLSTROM E; MAGNUSSON K-E; STENDAHL O; TAGESSON C
AUTHOR ADDRESS: DEP. MED. MICROBIOL., UNIV. LINKOPING, S-581 85 LINKOPING, SWED.
JOURNAL: EXP CELL RES 108 (1). 1977 175-184. **1977**
FULL JOURNAL NAME: Experimental Cell Research
CODEN: ECREA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Polymorphonuclear leukocytes [mammalian] were incubated at 37.degree. C with **liposomes** composed of phosphatidylcholine, cholesterol and dicetylphosphate and the cells obtained characterized with respect to properties that would disclose a **modification** of their surface properties. The cells excluded Trypan blue, did not leak 51Cr-labeled cytoplasmic proteins and responded as control cells to concanavalin A (ConA) with an increased HMS [hexose monophosphate shunt] activity. Their volume was increased as revealed by the pulse-height distribution at electronic counting. The partition of the cells in aqueous biphasic systems containing **polymers** with covalently bound ligands showed that their negative surface charge density and their liability to hydrophobic interaction were decreased. The cells showed a reduced capacity to phagocytose Salmonella typhimurium 395 MR 10 and S. typhimurium 395 MS opsonized with hyperimmune anti-MS IgG and a decreased random mobility. This suggests that the presence of exogenous lipid affects the molecular organization providing attachment of a particle to be phagocytosed and alters such surface properties of the cell that are linked to its motility. **Liposomes** may be used to **modify** the physico-chemical surface properties of polymorphonuclear leukocytes and so their essential biological functions.

1977

```
? s cell and division and liposom?
         3706584  CELL
          197864  DIVISION
           51255  LIPOSOM?
      S1     469  CELL AND DIVISION AND LIPOSOM?
? s s1 and glycoprotei?
             469  S1
          215658  GLYCOPROTEI?
      S2      17  S1 AND GLYCOPROTEI?
? rd
...completed examining records
      S3      17  RD (unique items)
? t s3/3,ab/all

 3/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12560277   21488952   PMID: 11602059
    The effect of p53 gene on p-glycoprotein expression and
chemotherapeutic cytotoxicity of hepatocellular carcinoma]
  Han Y; Liang L; Huang J; Ming W
  Department of Hepatobiliary Surgery, First Affiliated Hospital of Sun
Yat-sen University of Medical Sciences. Guangzhou 510080, China.
  Zhonghua gan zang bing za zhi = Zhonghua ganzangbing zazhi = Chinese
journal of hepatology (China)   Aug 2001, 9 (4) p237-9, ISSN 1007-3418
Journal Code: 9710009
  Document type: Journal Article ; English Abstract
  Languages: CHINESE
  Main Citation Owner: NLM
  Record type: Completed
  OBJECTIVE: To test the hypothesis that wild-type p53 regulates the
expression of p-glycoprotein . METHODS: Hep3B cells which lack the
expression of both p53 and retinoblastoma tumor suppressor genes because of
deletions, were transfected with a wild-type (wt) p53 cDNA and control
vector by a liposome method. RESULTS: After G418 selection, stable
wt-p53 transformants and control vector transformants (pNeo) were obtained.
Northern and Western blot analysis determined the expression of p53 mRNA
and protein in wt-p53 transformants, respectively. In wt-p53 transformants,
induction of transcriptionally active p53 was confirmed by the increase of
P21(waf1/cip1) protein. Levels of P-gp reduced in the cells expressing
wild-type p53 were linked to wt-p53 activity. Cytotoxicity assays revealed
that the wt-p53 transfectants were more sensitive to doxorubicin and
mitomycin compared with the pNeo transformants. Flow cytometry showed that
the accumulation of doxorubicin in wt-p53 transfectants was as 13 times as
that of the pNeo transformants. CONCLUSIONS: Restoration of wt-p53 activity
in Hep3B leads to sensitiveness to chemotherapeutic agents because of the
decrease of p-glycoprotein expression.


 3/3,AB/2     (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11331981   21385053   PMID: 11494411
  Macrophage depletion impairs oligodendrocyte remyelination following
lysolecithin-induced demyelination.
  Kotter M R; Setzu A; Sim F J; Van Rooijen N; Franklin R J
  Department of Clinical Veterinary Medicine, University of Cambridge,
Cambridge, UK.
  Glia (United States)   Sep 2001, 35 (3) p204-12, ISSN 0894-1491
Journal Code: 8806785
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
```

An association between macrophages and remyelination efficiency has been observed in a variety of different models of CNS demyelination. In order to test whether this association is causal or coincidental, we have examined the effects of macrophage depletion on the rate of remyelination of lysolecithin-induced demyelination in the spinal cord of young adult female rats. Macrophage depletion was achieved by reducing the monocyte contribution to the macrophages within the lesion using the clodronate-**liposome** technique. This technique not only resulted in a decrease in Ox-42-positive cells in the spleen of treated animals but also in the levels of macrophage scavenger receptor type B mRNA expression within the demyelinating lesion. In animals treated with clodronate-**liposomes** throughout the remyelination process, there was a significant decrease in the extent of oligodendrocyte remyelination at 3 weeks after lesion induction, but no effect on Schwann **cell** remyelination. If macrophage depletion was delayed until the second half of the remyelination phase, then there was no effect on the repair outcome, implying that macrophages are required for the early stages of CNS remyelination. The results of this study indicate that the macrophage response is an important component of successful CNS remyelination and that approaches to the treatment of demyelinating disease based on inhibition of the inflammatory response may also impair regenerative events that follow demyelination. Copyright 2001 Wiley-Liss, Inc.

3/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10739186 20273367 PMID: 10815920

Nuclear delivery of doxorubicin via folate-targeted **liposomes** with bypass of multidrug-resistance efflux pump.

Goren D; Horowitz A T; Tzemach D; Tarshish M; Zalipsky S; Gabizon A

Sharet Institute of Oncology, Hadassah Hebrew University Medical Center, Jerusalem, Israel.

Clinical cancer research : an official journal of the American Association for Cancer Research (UNITED STATES) May 2000, 6 (5) p1949-57, ISSN 1078-0432 Journal Code: 9502500

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Folic acid, attached to polyethyleneglycol-derivatized, distearoyl-phosphatidylethanolamine, was used to target in vitro **liposomes** to folate receptor (FR)-overexpressing tumor cells. Confocal fluorescence microscopic observations demonstrated binding and subsequent internalization of rhodamine-labeled **liposomes** by a high FR-expressing, murine lung carcinoma line (M109-HiFR cells), with inhibition by free folic acid. Additional experiments tracking doxorubicin (DOX) fluorescence with DOX-loaded, folate-targeted **liposomes** (FTLs) indicate that **liposomal** DOX is rapidly internalized, released in the cytoplasmic compartment, and, shortly thereafter, detected in the nucleus, the entire process lasting 1-2 h. FR-mediated **cell** uptake of targeted **liposomal** DOX into a multidrug-resistant subline of M109-HiFR cells (M109R-HiFR) was unaffected by P-**glycoprotein**-mediated drug efflux, in sharp contrast to uptake of free DOX, based on verapamil-blockade experiments with quantitation of **cell** -associated DOX and flow cytometry analysis. Delivery of DOX by FTLs to M109R-HiFR cells increased continuously with time of exposure, reaching higher drug concentrations in whole cells and nuclei compared with exposure to free DOX. The in vitro cytotoxic activity obtained with DOX-loaded FTLs was 10-fold greater than that of the nontargeted **liposome** formulation, but was not improved over that of free DOX despite the higher cellular drug levels obtained with the targeted **liposomes** in M109R-HiFR cells. However, if M109R-HiFR cells were exposed to drugs in vitro and tested in an in vivo adoptive assay for tumor growth in syngeneic mice along a 5-week time span, FTL DOX

was significantly more tumor inhibitory than free DOX. It is suggested that the biological activity of **liposomal** DOX released inside the cellular compartment is reduced in vitro due to the aggregated state of DOX, resulting from the **liposome** drug-loading process, and requires a long period of time and/or an in vivo environment for full expression.

3/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10576632 20118222 PMID: 10652629
Effect of mitoxantrone **liposomes** on multidrug-resistant breast cancer cells.
Poujol S; Tilleul P; Astre C; Martel P; Fabbro M; Pinguet F
Department of Oncopharmacology, Cancer Institute C.R.L.C., Montpellier, France.
Anticancer research (GREECE) Jul-Aug 1999, 19 (4B) p3327-31, ISSN 0250-7005 Journal Code: 8102988
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A major obstacle in efficacy of breast cancer chemotherapy is the emergence of multidrug resistance. We investigated modulation of multidrug resistance by **liposome**-encapsulated mitoxantrone in a drug resistant human breast MCF7R **cell** line and the influence of **liposome** composition. Neutral high phase-transition temperature and anionic low phase-transition temperature phospholipid **liposomes** , reduced the resistance factor from 142 to 15 and 38, respectively. The higher cytotoxicity obtained with mitoxantrone-encapsulation was not necessarily related to higher intracellular uptake. Our data suggest that **liposomes**, according to their lipid composition, may alter the P-**glycoprotein** function by plasma membrane stabilization and modulate multidrug resistance in human cancer.

3/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10478133 20004040 PMID: 10535382
Heparan sulfate chains with antimitogenic properties arise from mesangial **cell**-surface proteoglycans.
Wang A; Miralem T; Templeton D M
Department of Laboratory Medicine and Pathobiology, University of Toronto, Ontario, Canada.
Metabolism: clinical and experimental (UNITED STATES) Oct 1999, 48 (10) p1220-9, ISSN 0026-0495 Journal Code: 0375267
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Heparan sulfate (HS) chains accumulate in both the medium and the **cell** layer of mesangial **cell** cultures. When given in fresh medium to quiescent cultures at naturally occurring concentrations, they suppress entry into the **cell** cycle and progression to DNA synthesis. We have attempted to identify the proteoglycan (PG) source of the antimitogenic HS chains from mesangial **cell** layers (HS(c)) and medium (HS(c)). When cells were labeled for 16 hours with [35S]sulfate, 25% of the label was found in intracellular HS chains and 5% in extracellular HSPGs. **Cell** -surface HSPGs accounted for the remaining 70% of the label associated with **cell**-layer HS and were released by either trypsin or 2% Triton X-100. About 20% of this **cell**-surface fraction was released by treatment with phosphatidylinositol-specific phospholipase C (PI-PLC), and probably represents glypican-like PG; glypican mRNA was present in the

cells. The remainder of this fraction could be incorporated into **liposomes** , indicating the presence of hydrophobic transmembrane regions suggestive of syndecans. Upon purification and deglycosylation, an antiserum to rat liver HSPGs that reacts primarily with syndecan-2 showed a strong signal corresponding to this protein and three weaker bands that may represent additional syndecans. mRNAs for syndecan-1, -2, and -4 were present in the cultures. Syndecan-1 and -2 mRNAs were increased 30 minutes after stimulation of quiescent rat mesangial cells (RMCs) with serum. Heparin, HS(c), and HS(m) all prevented this increase. Syndecan-4 mRNA was not affected by serum, heparin, or HS. In pulse-chase experiments, the amount of 35S appearing in the cellular protein-free HS fraction was accounted for almost entirely by **cell** -surface PGs, as matrix-associated label was a minor contribution at the end of the pulse-labeling. The appearance of [35S]HS in **cell** extracts was unaffected by phospholipase C treatment, indicating that turnover of the newly labeled syndecan fraction is the source of the antimitogenic HS chains.

3/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10126674 99106987 PMID: 9891969
Liposome oligomannose-coated with neoglycolipid, a new candidate for a safe adjuvant for induction of CD8+ cytotoxic T lymphocytes.
Fukasawa M; Shimizu Y; Shikata K; Nakata M; Sakakibara R; Yamamoto N; Hatanaka M; Mizuochi T
Department of Preventive Medicine, Institute of Tropical Medicine, Nagasaki University, Sakamoto, Japan.
FEBS letters (NETHERLANDS) Dec 28 1998, 441 (3) p353-6, ISSN 0014-5793 Journal Code: 0155157
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The cytotoxic T lymphocyte (CTL) response has recently been shown to play a role in protection against human immunodeficiency virus (HIV) and it is therefore thought that a vaccine against HIV must be able to elicit a CTL response. The development of a safe, effective adjuvant is very important because alum, the only adjuvant available for use in humans at present, can barely induce a response of this type. We demonstrate here that **liposomes** that contain an immunodominant peptide (15 amino acids) of the envelope **glycoprotein** gp120 of HIV-1 and that are coated with mannopentaose-dipalmitoylphosphatidylethanolamine conjugate induce a major histocompatibility complex class I-restricted CD8+ CTL response in mice with a single subcutaneous immunization, whereas non-coated **liposomes** do not. Since no damage to the skin at the injection site was caused by the **liposomes**, and since the oligomannose-coated **liposomes** consist of innocuous materials ubiquitously distributed throughout the human body, they may be highly suitable for use as a safe adjuvant in vaccines inducing a CTL response against HIV.

3/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09915708 98351592 PMID: 9688306
Delivery to cancer cells of antisense L-myc oligonucleotides incorporated in fusogenic, cationic-lipid-reconstituted influenza-virus envelopes (cationic virosomes).
Waelti E R; Gluck R
Institute of Pathology, University of Bern, Switzerland. waelti@patho.unibe.ch
International journal of cancer. Journal international du cancer (UNITED

STATES) Aug 31 1998, 77 (5) p728-33, ISSN 0020-7136 Journal Code: 0042124
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Antisense oligodeoxy-nucleoside phosphorothioates (OPTs) of L-myc were encapsulated into reconstituted influenza-virus-A envelopes (virosomes). The envelopes of the virosomes consisted of a single positively charged (cationic) lipid bilayer. Binding of cationic virosomes to cellular receptors that are membrane **glycoproteins** or glycolipids containing terminal sialic acid is mediated by the hemagglutinin **glycoprotein** (HA) of the influenza virus. After internalization through receptor-mediated endocytosis, cationic virosomes fuse efficiently with the membranes of the endosomal-**cell** compartment, and as a consequence the encapsulated OPT are delivered to the **cell** cytoplasma. Examination by fluorescence microscopy of the cellular uptake of cationic virosomes containing fluorescein-labeled OPT showed rapid and efficient incorporation of virosomes. Addition of cationic virosomes (75-150 microl) containing antisense L-myc OPT in the picomolar range to small-**cell**-lung-cancer (SCLC) **cell** cultures that expressed highly the L-myc oncogene led to strong inhibition of thymidine incorporation in a concentration-dependent manner. Virosome-entrapped sense L-myc OPT and random-order OPT had only minimal effects on the thymidine uptake. Cells of SCLC **cell** line NCI-H82 expressing a very low level of L-myc were not affected by antisense-L-myc virosomes. In Western-blot analysis, expression of L-myc protein was suppressed in the antisense-virosome-treated NCI-H209 cells but not in untreated control NCI-H209 cells. These results suggest that cationic virosomes may have great potential as an efficient delivery system for antisense oligonucleotides in cancer therapy.

3/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09690430 98098554 PMID: 9436177
Developmental regulation of the effects of surfactant protein A on phospholipid uptake by fetal rat type II pneumocytes.
Kresch M J; Christian C
Department of Pediatrics, University of Connecticut Health Center, Farmington 06030-2203, USA.
Lung (UNITED STATES) 1998, 176 (1) p45-61, ISSN 0341-2040 Journal Code: 7701875
Contract/Grant No.: R29-HL49099; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Surfactant protein A (SP-A) enhances the uptake of phospholipid by type II cells derived from adult and late gestation fetal rat lung. The present study was performed to examine more fully the developmental biology of the effects of SP-A on phosphatidylcholine (PC) uptake, to determine the effect of SP-A on the cellular location of bound and internalized phospholipid and on the metabolism of internalized phospholipid by morphologically undifferentiated (18-day) and morphologically differentiated (19-day) fetal type II cells. SP-A enhanced uptake almost two-fold in a dose-dependent manner in 19-day fetal cells, but it had no effect on uptake by 18-day fetal cells at any concentration. Stimulation of uptake by 19-day fetal cells was saturable at concentrations above 1 microgram/ml SP-A. Maximal uptake was 1.12 nmol of PC/mg of protein, and the effective concentration that yields 50% maximal response, K phi, was 58.9 ng/ml (84.1 pM). The effect of SP-A on uptake by 19-day fetal cells was detectable as early as 1 min of exposure. Uptake correlated significantly with time both in the absence ($r = 0.98$, $p < 0.001$) and presence of 5 micrograms/ml SP-A ($r =$

0.979, p < 0.001). The rate of uptake in the presence of SP-A (0.019 +/- 0.002 nmol of PC/mg of protein/min) was twice the rate of uptake in controls (0.009 +/- 0.001 nmol of PC/mg of protein/min). SP-A had no effect on binding to plasma membranes and uptake of phospholipid into lamellar bodies by 18-day fetal cells. On the other hand, SP-A significantly enhanced binding of dipalmitoyl phosphatidylcholine to plasma membranes (two- to threefold) and uptake into lamellar bodies (threefold) of 19-day fetal cells. SP-A caused a significant reduction in the degradation of internalized phospholipid by differentiated fetal type II cells. Based on the lack of effect of exogenous SP-A on 18-day fetal cells, we conclude that the response to SP-A is under developmental control. SP-A enhances the initial binding to the plasma membranes of fetal type II cells and subsequent internalization into the lamellar bodies. This effect is associated with a protection of internalized phospholipid from metabolic degradation. Both of these processes are developmentally regulated during the transition from the canalicular to the saccular phase of lung development.

3/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09437955 97348951 PMID: 9204955

Liposome -associated interferon-alpha-2b functions as an anti-fibrogenic factor for human dermal fibroblasts.

Ghahary A; Shen Q; Rogers J A; Wang R; Fathi-Afshar A; Scott P G; Tredget E E

Department of Surgery, University of Alberta, Edmonton, Canada.

Journal of investigative dermatology (UNITED STATES) Jul 1997, 109 (1) p55-60, ISSN 0022-202X Journal Code: 0426720

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

This study was conducted to determine whether interferon-alpha-2b (IFN-alpha-2b) can be encapsulated in **liposomes** without compromising its anti-fibrogenic effects on human dermal fibroblasts. The rationale for this approach is that systemic administration of IFN-alpha-2b by injection for treatment of dermal fibrosis is uncomfortable, requires a large quantity of the cytokine, and cannot be easily used in children. **Liposomes** are potentially useful as vehicles for the topical delivery of drugs if they can be encapsulated without loss of biologic activity. Empty sonicated vesicles composed of dioleoyl-phosphatidylcholine:dioleoyl-phosphatidylglycerol at a molar ratio of 7:3 were mixed with various concentrations of IFN-alpha-2b and then dried and rehydrated. An enzyme-linked immunosorbent assay (ELISA) was used to determine the efficiency of encapsulation and the stability of the preparation under experimental conditions. Greater than 80% of added IFN-alpha-2b became associated with the **liposomes** and remained encapsulated for up to 5 d at 4 degrees C. The rate of release increased markedly at 37 degrees C. **Liposome** -encapsulated IFN-alpha-2b (2000 units per ml) significantly reduced the proliferation of dermal fibroblasts (60 +/- 8.8 vs. 100 +/- 8, mean +/- SEM, $p < 0.05$, $n = 8$) and the levels of mRNA for type I (41.5 +/- 8.7% vs 100 +/- 18, $p < 0.05$, $n = 4$) and type III (68 +/- 8.4% vs 100 +/- 4.9%, $p < 0.05$, $n = 3$) procollagen, as analyzed on northern blots. This was consistent with the reduction found in collagen in conditioned medium from treated fibroblasts. In contrast, treatment increased levels of mRNA for collagenase (241 +/- 42% vs 100 +/- 3.4, $p < 0.05$, $n = 3$) and collagenase activity (289 +/- 5.8% vs 100 +/- 10.9%, $p < 0.05$, $n = 9$) in conditioned medium. This last effect was probably not due to a reduction in TIMP-1 (tissue inhibitor of metalloproteinase-1) because levels of mRNA for this inhibitor were not lower in treated cells. The efficacy of **liposome** -associated IFN-alpha-2b in vitro supports the concept of the topical use of this anti-fibrogenic agent for treatment of fibroproliferative

disorders.

3/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09287691 97185144 PMID: 9032885
Immune responses in mice induced by HSV-1 **glycoproteins** presented with ISCOMs or NISV delivery systems.
Hassan Y; Brewer J M; Alexander J; Jennings R
Department of Medical Microbiology, University of Sheffield Medical School, UK.
Vaccine (ENGLAND) Dec 1996, 14 (17-18) p1581-9, ISSN 0264-410X Journal Code: 8406899
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The purpose of this study was to evaluate the immunogenicity of a herpes simplex virus type I (HSV-1) antigen preparation, obtained following zwitterionic detergent treatment of virus, and incorporation of the antigens into either immunostimulating complexes (ISCOMs) or non-ionic surfactant vesicles (NISV) delivery systems. Using Balb/c mice the ISCOM and NISV HSV-1 vaccines were assayed for their capacity to induce and enhance both the humoral and cellular immune responses, and to elicit protection against both homologous and heterologous virus challenge. The serum from animals vaccinated with either the NISV or the ISCOM HSV-1 antigen preparation, were found to contain high levels of total IgG and IgG1 and IgG2a subclass antibodies. In addition, both preparations were found to induce high neutralizing (NT) antibody levels following a two immunization protocol and to provide some protection against homologous and heterologous HSV challenge infection. Lymphoproliferative responses were observed in cultures of splenocytes from mice immunized with both HSV-1 NISV vaccine and HSV-1 ISCOMs vaccine, following various antigenic stimuli in vitro. In general, these were most marked in animals immunized with the HSV-1 NISV preparation, and particularly so when the splenocytes were stimulated in vitro with live HSV-1. Both the NISV and ISCOM HSV-1 vaccines were found to have induced interleukin 2, interleukin 10 and interferon-gamma in spleen **cell** culture supernatants, although again, the highest responses in general were observed in supernatant fluids from spleen **cell** cultures from animals immunized with the HSV-1 NISV preparation. These results suggest that a wide range of immune activity can be elicited by HSV-1 antigens presented to the immune system of mice in these formulations.

3/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08949964 96302453 PMID: 8688320
Daunorubicin and doxorubicin but not BCNU have deleterious effects on organotypic multicellular spheroids of gliomas.
Kaaijk P; Troost D; de Boer O J; Van Amstel P; Bakker P J; Leenstra S; Bosch D A
Department of Neurosurgery, University of Amsterdam, Graduate school Neurosciences Amsterdam, The Netherlands.
British journal of cancer (SCOTLAND) Jul 1996, 74 (2) p187-93, ISSN 0007-0920 Journal Code: 0370635
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In the present study organotypic multicellular spheroids (OMS) were used to study the effects of chemotherapeutic agents on malignant gliomas.

Compared with the frequently used **cell** line models, OMS have several advantages with respect to the preservation of the cellular heterogeneity and the structure of the original tumour. OMS prepared from seven glioma specimens were treated with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), daunorubicin or doxorubicin. After exposure to these drugs, the histology and **cell** proliferation of the OMS were analysed by immunohistochemistry and image analysis. Furthermore, the expression of P-**glycoprotein** (P-gp) and multidrug resistance-related protein (MRP), which both can contribute to resistance to daunorubicin and doxorubicin, were immunohistochemically investigated. We found that OMS from gliomas are sensitive for daunorubicin and doxorubicin but not for BCNU in terms of tissue destruction and decrease in **cell** proliferation. In addition, all gliomas were P-gp and MRP negative, which is in accordance with the sensitivity for daunorubicin and doxorubicin. Considering the potential use of several new alternative drug delivery methods, such as intratumoural implantation of drug-impregnated polymers or **liposomal** encapsulation of cytostatic drugs, daunorubicin and doxorubicin might be effective in the treatment of malignant gliomas.

3/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08695994 96059374 PMID: 7583102

Density-dependent regulation of **cell** growth by contactinhibin and the contactinhibin receptor.

Gradl G; Faust D; Oesch F; Wieser R J
Institute of Toxicology, Mainz, Germany.

Current biology : CB (ENGLAND) May 1 1995, 5 (5) p526-35, ISSN 0960-9822 Journal Code: 9107782
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

BACKGROUND: The number of cells within mammalian tissues is maintained by growth-stimulating and growth-inhibiting mechanisms, with inhibitory signals being superimposed over growth stimuli. This is reflected, in the culture of normal adherent cells, by the phenomenon of density-dependent inhibition of growth: cells cease proliferation after becoming a confluent monolayer. We have shown previously that a plasma membrane **glycoprotein** , contactinhibin, is a major effector of negative growth regulation. Although transformed cells express contactinhibin in a functionally active form, they are not growth-inhibited, suggesting that the defects that lead to their aberrant growth are located 'downstream' of contactinhibin. RESULTS: Here, we provide evidence that a 92 kD plasma membrane protein, which we call CiR, binds specifically to contactinhibin and acts as a receptor mediating the contact-dependent inhibition of growth of cultured human fibroblasts. When polyclonal antibodies against CiR were introduced into cells using **liposomes**, confluent cells were released from density-dependent growth control. By contrast, cross-linking CiR that is localized to the plasma membrane, using anti-CiR antibodies, led to growth inhibition, suggesting that CiR is a signalling molecule and implicating CiR oligomerization in signal generation. This conclusion is supported by the finding that binding of contactinhibin by CiR is strongly dependent on the local concentration of both molecules and has a sharp threshold. When CiR was isolated by immuno-precipitation under conditions favouring phosphorylation, it was hyperphosphorylated on serine and threonine residues and had reduced contactinhibin-binding capacity; the binding capacity of CiR was restored after treatment with potato acid phosphatase. Fibroblasts transformed with simian virus 40 had reduced CiR expression, higher CiR phosphorylation levels, and a strongly reduced capacity of CiR to bind to contactinhibin. Phosphatase treatment of the CiR isolated from transformed cells only partially restored its contactinhibin-binding capacity. CONCLUSIONS: Homeostasis is the net result

of a highly balanced network of growth-stimulating and growth-inhibitory signals. We have shown that density-dependent inhibition of growth in vitro is mediated by the interaction of contactinhibin with a 92 kD plasma membrane **glycoprotein** , CiR, the contactinhibin-binding capacity of which is regulated by phosphorylation.

3/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08564464 95322200 PMID: 7541229
(Patho)physiologic pathways to drug targeting: artificial viral envelopes.
Schreier H; Ausborn M; Gunther S; Weissig V; Chander R
Center for Lung Research, Vanderbilt University, School of Medicine, Nashville, Tennessee 37232-2650, USA.
Journal of molecular recognition : JMR (ENGLAND) Jan-Apr 1995, 8 (1-2) p59-62, ISSN 0952-3499 Journal Code: 9004580
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The goal of this study was to exploit molecular recognition of **cell** surface receptors by viral surface **glycoproteins** as a means for the selective intracellular delivery of macromolecules. To accomplish this, artificial viral envelopes (AVE) resembling the human immunodeficiency virus-1 (HIV-1) were designed as a model system. Recombinant HIV-1 surface **glycoprotein** gp160 (HIV-1 rgp160) was inserted in the artificial envelope by a two-step detergent dialysis process. The artificial HIV-1 envelope recognized the CD4 **cell** surface receptor. FITC-dextran and ricin A were employed as model macromolecules as they cannot passively diffuse across **cell** membranes. Selective transfer of FITC-dextran encapsulated in HIV-1 rgp160 AVE into a CD4-positive **cell** line (REX-1B) versus a CD4-negative **cell** line (KG-1) was demonstrated. Ricin A at concentrations as low as 2 ng/ml arrested **cell** growth of CD4-positive MOLT-4 cells, whereas 8 ng/ml ricin A in solution had no effect on **cell** growth. The arrest of **cell** growth was reverted in the presence of excess anti-gp120 monoclonal antibody. Naked envelopes (without HIV-1 rgp160 inserted) were also found to interact with cells and transfer material, although less efficiently and in a non-specific manner. Viral mimicry using AVE may be a means for targeted intracellular delivery of peptides, proteins, enzymes, toxins, oligodeoxynucleotides, gene constructs, and other non-diffusive, labile or toxic macromolecules.

3/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08558364 95315234 PMID: 7794945
Collateral sensitivity of multidrug resistant cells to narcotic analgesics is due to effects on the plasma membrane.
Callaghan R; Riordan J R
Research Institute Hospital for Sick Children, Toronto, Ontario, Canada.
Biochimica et biophysica acta (NETHERLANDS) May 24 1995, 1236 (1) p155-62, ISSN 0006-3002 Journal Code: 0217513
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
It has previously been demonstrated that opiates interact directly with P-**glycoprotein** in drug resistant Chinese hamster ovary (CHO) cells (Callaghan, R. and Riordan, J.R. (1993) J. Biol. Chem. 268, 16059-16064). In this study we have examined the effects of several opiates on the growth of drug sensitive and resistant CHO and human MCF7 **cell** lines. The

growth of P-**glycoprotein** expressing cells was inhibited by the opiates pentazocine, pethidine and naloxone to a greater extent than in drug sensitive cells. Since P-**glycoprotein** is localised at the plasma membrane the effects of opiates on membrane biophysical properties were investigated. The opiates caused a fluidizing effect in membranes from P-**glycoprotein** expressing cells and decreased the basal level of P-**glycoprotein** phosphorylation. In addition, they were able to increase the leakage of the membrane impermeant compound 6-carboxyfluorescein entrapped in model membrane vesicles. The ability to alter membrane biophysical properties correlated with the inhibitory effects on growth of drug resistant cells. These results suggest that the collateral sensitivity of P-**glycoprotein** expressing **cell** lines to opiates is mediated by the drugs' effects on the plasma membrane.

3/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06484746 90180487 PMID: 2155629
Isolation from chick somites of a **glycoprotein** fraction that causes collapse of dorsal root ganglion growth cones.
Davies J A; Cook G M; Stern C D; Keynes R J
Department of Anatomy, University of Cambridge, England.
Neuron (UNITED STATES) Jan 1990, 4 (1) p11-20, ISSN 0896-6273 Journal Code: 8809320
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The segmented pattern of peripheral spinal nerves in higher vertebrates is generated by interactions between nerve cells and somites. Neural crest cells, motor axons, and sensory axons grow exclusively through anterior-half sclerotome. In chick embryos, posterior cells bind the lectins peanut agglutinin (PNA) and Jacalin. When **liposomes** containing somite extracts are applied to cultures of chick sensory neurons, growth cones collapse abruptly, recovering within 4 hr of **liposome** removal. Collapse activity is eliminated by immobilized PNA, and SDS-PAGE demonstrates two major components (48K and 55K), which are absent from anterior-half sclerotome. Rabbit polyclonal antibodies against these components recognize only posterior cells and may also be used to eliminate collapse activity. We suggest that spinal nerve segmentation is produced by inhibitory interactions between these components and growth cones.

3/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05684212 88113757 PMID: 3428926
In vitro cellular immune response to measles viral **glycoproteins**: role of the antigen vector.
Bakouche O; Mougin B; Gerlier D
INSERM U. 218, Centre Leon Berard, Lyon, France.
Immunology (ENGLAND) Dec 1987, 62 (4) p605-11, ISSN 0019-2805 Journal Code: 0374672
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The capacity of measles virus and haemagglutinin (HA) and fusion (F) **glycoproteins**, presented either as soluble antigens, associated with **liposomes** or as Iscoms, to induce an in vitro primary and anamnestic cellular response was studied in syngeneic W/Fu rats using the MTT colorimetric assay. A primary cellular response was observed when the

virus, HA + F **liposomes** or HA + F Iscoms were used as immunogens, but not when soluble HA + F **glycoproteins** were used. The irradiation of the naive spleen cells at 500 rads allowed the generation of a primary response with the soluble antigens. All these primary responses were low, of similar intensity and dose-dependent. The responses were stronger after the stimulation of spleen cells from seropositive immune rats with virus, HA + F **liposomes** or HA + F Iscoms, whereas they were moderate after stimulation with soluble HA + F. In addition, far less antigenic material was required and the use of a vehicle for HA + F (**liposomes**, Iscoms) dramatically lowered the threshold of the sensitivity to the antigens. The immunization of rats with soluble HA + F **glycoproteins** resulted in the anergy of their spleen cells even to virus, HA + F **liposomes** or HA + F Iscoms. Again, irradiation of these cells could restore their ability to elicit a primary response to any type of HA + F immunogens. Using the lysosomotropic Leu-0-Met agent, all the cellular responses were found to be accessory cells dependent, the responses being restored after supplementation with 10% peritoneal exudate cells from naive rats. These treatments did not break the immunosuppression induced by soluble HA + F **glycoproteins** . The uptake of the various immunogens by the murine macrophage **cell** line J774-1 was also studied using radioactively labelled virus and HA + F **glycoproteins**. The uptake of soluble HA + F was limited to 10-15%, whereas that of the other immunogens was almost complete. The data reported indicate that the modification of the supramolecular architecture of HA + F **glycoproteins** by their presentation in **liposomes** or Iscoms could modulate their immunogenicity, both qualitatively and quantitatively. It could prevent the generation of a radiosensitive suppressive mechanism, increase the sensitivity to the antigen and the activation level of the responding **cell** population. Quantitative modifications are accessory **cell** dependent and initiated within the first hour of the stimulation.

3/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04630626 85007097 PMID: 6332814
Growth-inhibitory activity of lymphoid **cell** plasma membranes. II. Partial characterization of the inhibitor.
Stallcup K C; Burakoff S J; Mescher M F
Journal of cell biology (UNITED STATES) Oct 1984, 99 (4 Pt 1) p1227-34, ISSN 0021-9525 Journal Code: 0375356
Contract/Grant No.: AI-17258; AI; NIAID; CA-14723; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

We have shown that plasma membranes from lymphoid cells have inhibitory activity for the growth of normal lymphocytes and lymphoid tumor cells (Stallcup, K. C., A. Dawson, and M. F. Mescher, J. **Cell** Biol. 99:1221-1226). This growth-inhibitory activity has been found to co-purify with major histocompatibility complex class I antigens (H-2K and D) when these **cell** surface **glycoproteins** are isolated from detergent lysates of cells by affinity chromatography on monoclonal antibody columns. When incorporated into **liposomes**, the affinity-purified H-2 antigens inhibited the growth of both normal lymphocytes and tumor cells at concentrations of 1-3 micrograms/ml. Inhibition was readily reversed upon removal of the **liposomes** from the **cell** cultures, even after several days of exposure of cells to the inhibitor. Inhibitory activity was insensitive to protease digestion or heat treatment, indicating that it was not due to the H-2 **glycoproteins** . This was confirmed by the demonstration that inhibitory activity could be separated from the H-2 protein by gel filtration in the presence of deoxycholate and could be extracted from membranes or H-2 antigen preparations with organic solvents. The results demonstrate that the growth-inhibitory component(s) of the

plasma membrane is a minor lipid or lipid-like molecule which retains activity in the absence of other membrane components. The findings reported here and in the preceding article suggest that this novel membrane component may have a role in control of lymphoid **cell** growth, possibly mediated by **cell** contacts.
?